NAMELESS INVARIANTS IN PSYCHOLOGICAL MEDICINE

JOHN COLLINSON
L.R.C.P.E.
FORMERLY JUNIOR MEDICAL OFFICER,
ROYAL MENTAL HOSPITAL, MONTROSE

PSYCHIATRY as a whole has its roots, historically and socially, in clinical medicine, and has accepted the empirical methods which a therapeutically directed discipline imposes. Psychology on the other hand, has its origin in philosophy: and for its development it has used the methods of the physical sciences, though it has sometimes failed to attain their standard of objectivity. The psychologist (in this country at least) has never faced the need for empiricism which therapeutic responsibility brings, and it often seems that this has exaggerated his flight into pure science.

Between empirical necessity and abstract rationality, it may be argued, stands the formal, intensive psychotherapist, typified by the psychoanalyst. It is perhaps not unfair to say that psychoanalysis had its origins in an acknowledged therapeutic impotence, which allowed the physician to observe and theorise—since by common consent he could not usefully act otherwise—in terms of that human experience to which, as a responsible clinician, he had access.

It therefore seems logical to suggest that psychiatry and psychoanalysis have common origins in clinical experience, and have diverged in aim—on the one hand, through therapeutic furor to empirical relief (through modification of symptoms) of the anxieties of those (relatives, neighbours, doctors, and nurses) who are in closest contact with the patient; and, on the other hand, through passive detached observation (Freud's " evenly hovering attention ") to a rather unusual uniformity of therapeutic method which almost entirely excludes acknowledged medical methods.

But although psychoanalysts and psychologists both claim to operate scientifically, they have started from different sets of data by reason of the analyst's privileged access to clinical material, not in the first place susceptible of analysis in terms of the rarified numerical or statistical abstractions so dear to the heart (or perhaps rather so close to the cortex?) of the psychologist, zealous for nothing less than measurable certainty.

It remains substantially true that the psychiatrist's empirical means of handling major psychoses and analytic views on the structure of human experience remain unhappily disparate from objective tests of behaviour, with the mathematical techniques of handling them, and psychological emphasis on statistical reliability.

With the advent of cybernetics, particularly communication theory and the theory of decision processes, a terminology has developed which offers the means of discussing many aspects of these three disciplines (among others) in common terms. It is hoped in what follows to illustrate this possibility with some fragments of cybernetic speculation.

* * *

The lines of thought which follow were suggested by the work of Hebb (1949).

Hebb's work seems to have been interpreted in many ways, which is, perhaps, ironically appropriate, in that it is designed to demonstrate possible nervous mechanisms capable of uniting apparently diverse phenomena under one conceptual head. His scheme appears to be one of great suppleness, elegance, power, and generality. It is designed as a speculative physiological basis capable of providing an intelligible account of " image, expectancy, need, and interest ", and " set, attention, insight, purpose, attitude, hypothesis, intention, vector, perseveration, preoccupation ", and which will also cover the main facts of perception and learning. The crux of the matter, says Hebb, lies in the nature of the concept, speaking physiologically, and of its relation to perception and learning, and he adds: " The essential need is to find out how to handle thought and related processes . . . there is no phase of psychological theory in which the same central weakness does not appear ".

The fundamental importance of " expectancy " to the life of the individual has also recently been underlined by Thorpe (1956a) in his extensive comparative review of instinct and learning in animals.

Hebb's speculative basis consists of the " phase sequence of cell assemblies ". The function of the phase sequence is to isolate common properties from primary data, with, he says, the possibility of stating clearly in physiological terms the meaning of words like " abstraction " or " similarity "—and, I would add, of words like " unconscious equivalence ". Hebb's " cell assembly " does indeed seem to function as a computer of conditional probability matrices, in a way which Mackay (1956) has suggested the nervous system is likely to do.

There seem to be grounds for suggesting that a mechanism which can do this would provide a possible physiological basis for some features of psychoanalytic theory, such as ego function, the existence of psychosexual stages of development, and the validity of statistically unreliable, non-reproducible, non-predictive procedures. The suspicion that this may be so has been strengthened by some general remarks by Bowlby (1952).

If I have understood Hebb's ideas correctly, they are at least in part closely related to the question of " stimulus equivalence ", which has occupied psychologists for a generation at least, and perhaps, under the guise of " universals ", for much longer. The subject is important because well-defined hypotheses on paper, as well as models in hardware, are now available which seem to go a long way towards offering solutions of the fundamental problem.

Pitts and McCulloch (1947), for instance, describe the detection of " equivalent apparitions related by similarity and congruence, like those of a single physical thing seen from various places, the equivalent apparitions sharing a common figure, and defining a group of transformations that take the figure into one another but preserve the figure invariant ". At least one machine which seems to possess some of the necessary properties for this sort of work is now available commercially.* Such models lie for the most part in the province of electrical engineering, but also within the territories of psychology and neurophysiology (Pitts and McCulloch 1947, Culbertson 1948, Uttley 1955, Deutsch 1956, Taylor 1956, 1958). Psychiatry is as yet little represented in the field, though some psychiatrists are now beginning to find that pure and symbolic logics find a place in fundamental theory (Bateson et al. 1956, Matte-Bianco 1959); and since the days of Boole

* Electronic Reading Automaton made by Solartron, Thames Ditton.

logicians have been interested in mechanising their subject (Jeffress 1951).

The notion of the validity of statistically unreliable ideas is strengthened by a suggestion due to Cronbach (1954) and supported to some extent on apparently different grounds by Ashby (1958).

Cronbach discusses the relations of the alien powers of Psychometrika and Clinicia. Thus:

" The natives of Clinicia are busy and happy, but regrettably unchastened by the stern and moral truths of our (Psychometrikan) civilisation. Psychometrika is noted chiefly for its output of . . . incomprehensible formulas and unfavourable book reviews . . .".

On the other hand ". . . the shores of Clinicia are an alluring tropical paradise . . . many founders of Clinicia came from Vienna and have imbued its institutions with the cheerful air of a *Mitteleuropäischer Kaffeeklatsch*. Clinicia has developed a language of great poetic beauty and obscurity . . ."

" No Psychometrikan can hear without a thrill of pride our motto ' If anything exists, it can be measured '. Some flaunt the more brazen slogan ' If something cannot be measured, it does not exist ! ' "

Cronbach recalls the rival schools of Ockham and Duns, and finds his Jungian enantiodromia or " middle way " piquantly enough in the information theory of Shannon and Weaver (1949).

This theory, formulated for the study of communications engineering, then taken over for the purposes of cerebral engineering, is now developed by a heterogeneous and growing band of cyberneticists. Cronbach recalls:

" We run two kinds of risk: of accepting a hypothesis when it is untrue, of rejecting it when it is true. Ockham said in effect that he was willing to risk any amount of error of the second kind, provided he could set an infinitesimal P-value on the risk of error of the first kind."

But we now know that the choice of risks is a matter of research strategy in a particular situation. Shannon's theory points out that a communications device—and a psychometric test is one—can be evaluated in terms of bandwidth and fidelity. Bandwidth refers to the number of messages a channel carries, or the number of questions a message can answer. According to Shannon we increase one (bandwidth or fidelity) at the expense of the other.

Cronbach concludes: " It is worth sacrificing fidelity to obtain optimal bandwidth. An interview gives fallible answers but it compensates by increased bandwidth." But, says Cronbach, bandwidth can also be too wide.

This point has been put in clinical terms by Gillhespy and Ratcliffe (1956) in discussing the effectiveness of treatments in parkinsonism: " Tests imply an artificial environment . . . the patient as a whole is a matter for clinical judgement." It is also mentioned in passing by Stanton et al. (1954) in writing of the informal structure of the mental hospital as a therapeutic institution. Lorenz (1950) has developed similar ideas in relation to animal studies, as has Chance (1957).

Ashby, also using (in part) a theorem due to Shannon, comes to like-sounding conclusions.

He refers, as a scientist, to the limitations of the scientist, and discusses the attitude of those who adopt the methods, but not the standards, of the physical sciences. He too recalls the strategies of operational research, of which he says " its first characteristic is that its aim is not understanding, but the purely practical one of control ". His further development of the theme is forcibly reminiscent of Ruesch and Bateson's (1951) psychoanalytic colleague, who complained that the more he practised, the less he could describe what he did; the chagrin of Glover (1955) whose questionnaires on psychoanalytic technique failed to reveal superficial similarities in analysts' descriptions of what they did; and perhaps also the faintly plaintive tones of Alexander and French (1946) who found that patients were not scientific in their response to " standard technique ". Ashby's plea for the acceptance of limitations has a roundly psychoanalytic ring.

Cronbach's remarks might be related to the suggestion that the information-handling capacity of the nervous system increases under certain conditions disproportionately with the " metrical content " (Mackay 1956) or the number of dimensions of information—for example, that more information can be handled in two sensory modalities simultaneously than by both separately (Sluckin 1958)—and it seems possible that these suggestions might represent some need, in terms of statistical analysis of variance, to confound a relatively large number of whatever experimental variables are adopted in studying behaviour. On this view, it might well be at once perfectly scientific and at the same time, humanly speaking, quite inadequate, to measure any number of apparently independent psychological variables.

It is suggested that the psychologist who insists on being " scientific ", no matter what the cost, must content himself with a sort of proof by enumeration of cases.

" This ", he may say, " I have done; and this, and this, and this." Any intuitionist will quite logically retort forever that this is not enough.

" You have missed something out," he may cry. " And I know that I cannot ever, scientifically speaking, show you what it is you have missed." " But ", he might add, " I can tell you why I cannot tell you: it is because of my enormous frequency-bandwidth, it is because of the size of my phase-sequences." If of a psychoanalytic persuasion he may say: " I deal in preverbal material, in primary symbols " (Money-Kyrle 1956) or equally: " I work in terms of ' R ', the total response " (Little 1957). Perhaps here and there, with less pretence, and with vulgar disregard for science, some might confess to a simple liking for working with people.

It must seem, it is true, that there can be no decision process for settling this sort of dispute; but we are in good company, for there is none after all for the whole of mathematics (Turing 1954). The therapist's claim, however logically unassailable, cannot be put to a logical test. It must remain undecided, his hypotheses logically untestable and therefore " unscientific ". For many, the scientist's cry of " Go to, I will see what I can do " may have a braver ring; but, in terms of common experience, it must seem that there will always be a need for artistry —and not least even in the purest of the sciences.

* * *

The development of these ideas was suggested (mirabile dictu) in the course of a discussion on the relation of psychoanalytic thought to institutional religion. The relevant material emerged from Rickman's (1957) analysis of Quaker practice in terms of Kleinian psychoanalytic theory. Rickman, himself a Quaker, was struck by forcible similarities between the Society of Friends and the psychoanalytic movement, as anyone familiar with both disciplines is likely to be. This observation was followed by an account of the properties of the " archetype ", an entity which lends itself, incongruously enough, to development in terms of the phase-sequences of Hebb.

The crux of the matter lay here in the description by successive speakers of similar concepts, each related to the communication of subjective experience, and each in a language congenial to the individual, so that it seemed that there was a sort of synonymy of experience behind the confusion of tongues, akin, it seemed, in the emotional

sphere, to the sort of perceptual transformations referred to by Pitts and McCulloch. It was this which led to consideration of the incommunicability of experience solely in scientific terms—a condition described, for instance, by Polanyi (1958): " No possible assertion can have more fundamental credentials than the conviction of its author ", by Weiss (1957): " No experience is so compelling as the individual's awareness of his own existence "; and by Micklem: " some inward touch of the heavenly fire at once incommunicable to others and self-evidencing to oneself ".

Such considerations have seemed appropriate both to certain aspects of psychotherapy and to one of the approaches to the study of religion, that is to say the approach which is properly and in a strictly technical sense called " mystical ". It is of some interest that this word " mystical " should be in common use in another sense, as a simple vague term of near-obscene abuse, applied, among other things, to the study of intensive psychotherapy. Those to whom the term applies in its strict, technical sense, are more often than not unusually shrewd, hard-headed, and business-like—" When a Quaker calls you ' Dear Friend ' it is time to guard your chin " (Richardson 1957). Certainly some invasion of psychiatric thought by philosophically and theologically minded workers is going on—an invasion which may or may not be beneficial to psychiatric thinking.

The relevance of the " mystical " approach to the practice of psychotherapy has seemed to lie fundamentally in its relation to the structure of experience (as opposed to the study of behaviour), but more particularly in its emphasis on the essential namelessness of individual experience.

It must be argued, on the contrary, that each of us has a nervous system much like his neighbour's, and that each of us is likely to structure his experience in similar ways, be they in terms of the classical stages of psychosexual genesis, or of archetypes, or in any other terms. From the point of view of the scientist—the non-participant observer—these constants, these invariants of human nature may certainly be given verbal tags, being abstracted from a broad generality of the observer's experience with his fellows, often by dint of great labour and the application of highly sophisticated techniques; but so smudging the outlines of the particular individuals who make up the observer's research material. (Abstraction, that is to say, involves loss of identity. One may be sensitive or selective, but, exactly as with bandwidth and fidelity, the one to some extent necessarily excludes the other.)

But the psychotherapist cannot by any means be a mere indifferent expert, a simple technician in human affairs. The man who is concerned about the experience of his client is not only a man endowed *ipso facto* with a counter-transference, but a man who is likely to be perceived by his patient as a human being in the fullest (and, alas, quite undefinable) sense of the world. He is a participant observer, involved in the situation; he knows that " no manne is an ilande ". Bockoven (1958), for example, has thrown some light on this aspect of the situation with the discovery that it is possible to relieve the distress of intoxication with hallucinogenic drugs by psychotherapy, but only when the therapist abandons any preconceived rules and reacts spontaneously, his alarm at the subject's distress, so to speak breaking bounds.

* * *

Any discussion of behaviour, to be of use as such in the therapeutic situation, must be communicable to the patient, and this rules out, at least in the early stages, most technical (scientific, " objective ", non-participant) explanation, whether in terms of neurophysiology or " complexes ". For technical abstractions, generalisations, concepts, invariants become available in the first place only through concrete particular examples—a process explored, for instance, in the perceptual field by Piaget. It is well known that concrete thinking is characteristic of children, defectives, and schizophrenics.

But the patient, sore beset by particular experiences with which he cannot deal, necessarily lacks the objectivity, the span of apprehension, the strength of ego activity to stand aside from his experiences, or to consider them, group them, organise them, and give them a name.

It would be trite to stress unduly how each of us lives out his life in a unique environment, however we may ultimately relate our experiences to the fundamental invariants of human nature. And in this lies in part the relevance of the intuitive or empathetic approach (Mayer-Gross et al. 1954). For to the patient, unable to accept his own experience of his own existence, scientific " non-participant " objectivity cannot in the first place represent his experience, which is much too immediate and overwhelming. Any subjective experience must in the first place be dealt with in terms of " denotation " rather than " connotation ": concretely that is, and not abstractly. This is akin to what happened in the original discussion which prompted these reflections: it seemed that each speaker described similar concepts, each in the language congenial to him, whence the " synonymy of experience " already referred to.

Something like this, it is suggested, makes up a large part of the need in analytically oriented psychotherapy for " working through ", that is the elaboration and definition of a patient's underlying " complexes "—which will in the deepest levels be common to his fellows—in terms of his own experiences peculiar to himself. This working through will then constitute a learning situation quite analogous to one of the situations for which Hebb developed his approach, and as this situation progresses, the patient will become more aware of the way in which his particular thoughts and feelings are organised. So too, as the process of psychotherapy goes on, the patient will become aware of his essential humanity, and communication between therapist and patient will become more informative, efficient, and economical. But there will always be some residual " noise " in the communication channel between therapist and patient, and something like this no doubt lies at the back of the continuing profusion of psychological schools and terminologies. Such an approach may also account in part for the time usually necessary for any really intensive psychotherapy, and for the increasing time necessary in older patients. It is mercifully not yet clear what the cybernetic analogue of " resistance " may be, though Ostow (1957) would have it arise in that fashionable seat of mystery, the temporal lobe.

* * *

Hebb's speculative physiological basis for thinking has as one of its features exactly the provision of a clear account of words like " similarity ", " synonymy ", and " equivalence " in terms of nervous function. It gives an account of how the nervous system might handle sets of data with common features, and thence how isolated data might

evoke in the nervous system, in a strongly established phase-sequence, the neural representations of the concepts, gestalten, configurations, needs, drives, motives, equivalents, or whatever, with which such data are associated or to which they belong.

By way of example, the mature nervous system of a sufficiently highly evolved animal will recognise as one triangle any three objects or three linear boundaries no matter (within limits) how placed. But the logic of this little matter is probably very advanced. There is after all no such thing as " the triangle " (just as there are no diseases, only sick people). Nothing logical is ever perceptible.

That the nervous system should be able to compute invariants, abstractions, generalisations, in this way is not, it is argued, less startling in principle than to say that the nervous system at some level may make pedantry, parsimony, and petulance " equivalent " to persistent contraction of the external anal sphincter, in terms of fixation at the classical anal-retentive stage of psychosexual genesis.

But the question does arise as to how far, in what ways, and under what circumstances it is desirable to generalise about human experience. To recapitulate: it is a commonplace that each individual's experience is unique—a consideration emphasised indirectly by Bexton, Heron, and Scott (1954) whose work on sensory deprivation has thrown into relief the tremendous dependence of mental function on the environment, due no doubt ultimately to the evolutionary position of man and the corresponding adaptability of his nervous system. Experience becomes capable of being put in general terms only as we cease to be involved in it. But there is some limit to the extent to which we can become " objective " about and uninvolved by our own behaviour—in alternative terms, there is a limit to the size of our phase-sequences. In Ashby's terms our channel capacity is finite. In the last analysis logic breaks down. We must " be ourselves ", we must accept primary instinctual data as such or break down ourselves. We must, like the centipede in the ditch, be able simply to " behave ". In doing so we can work at the limits of the " ego boundary "; we can work, perhaps, at the optimal frequency bandwidth. We can live and work in terms of Little's " total response ". In the familiar vague evocative terms of popular psychology our nervous system is " integrated ". There is then the least possible dissociation, the least possible operation at primitive levels of disorganisation.

* * *

All these things, put in the language of ego psychology, use also the language of cybernetics. Organisation, pattern, probability, discrimination, decision are all terms common to psychoanalytic theory and to cybernetics. They are indeed common to wider fields than this. Thorpe (1956b), for instance, in his review of instinct and learning in animals, finds the drive towards patterning and organisation of perceptions to be a fundamental necessity, in distinction, however to the earlier attitude of Fenichel (1945) in an admittedly more complex field. And Sawyer (1955) for his part points out that pattern is of the very essence of mathematical thinking in particular and of vital activity in general—which is perhaps, after all, only to echo Thorpe. Alexander (1958) has also drawn attention to the rewards of thinking in terms of organisation and negative entropy, and also seeks to relate a theory of neurosis to communication theory, rather as Bateson et al. (1956) seek to relate the schizophrenic ego defect to Russell's logical types.

We cannot quantify psychodynamics, but it is beginning to appear that these coincidences of language are more than accidental, more, too, than due to meaningless breadth of terminology. In principle at least, we should yet find some more adequate working model of psychic function, within whatever our limitations may turn out to be.

I should like to thank the library of the Royal College of Physicians of Edinburgh for invaluable bibliographical help.

REFERENCES

Alexander, F. (1958) *Behavior. Sci.* **3**, 293.
— French, T. M. (1946) Psychoanalytic Treatment. New York.
Ashby, W. R. (1958) *Cybernetica*, **1**, 83.
Bateson, G., Jackson, D. D., Haley, J., Weakland, J. (1956) *Behavior. Sci.* **1**, 251.
Bexton, W. H., Heron, W., Scott, T. H. (1954) *Canad. J. Psychol.* **8**, 70.
Bockoven, J. S. (1958) *Arch. Neurol. Psychiat.* **80**, 520.
Bowlby, J. (1952) *in* Prospects in Psychiatric Research (edited by J. M. Tanner); p. 69. Oxford.
Chance, M. R. A. (1957) *Lancet*, ii, 687.
Cronbach, L. J. (1954) *Psychometrika*, **19**, 263.
Culbertson, J. T. (1948) *Bull. math. Biophys.* **10**, 97.
Deutsch, J. A. (1956) *Brit. J. Psychol.* **47**, 115.
Fenichel, O. (1945) Psychoanalytic Theory of Neurosis; p. 13. London.
Gillhespy, R. O., Ratcliffe, A. H. (1956) *Birm. med. Rev.* **19**, 115.
Glover, E. (1955) The Technique of Psychoanalysis. London.
Hebb, D. O. (1949) The Organisation of Behavior. London.
Jeffress, Ll. A. (1951) Cerebral Mechanisms in Behavior; p. 106. London.
Little, M. (1957) *Int. J. Psycho-Anal.* **38**, 240.
Lorenz, K. (1950) *in* Symposia of Society of Experimental Biology; vol. IV. Cambridge.
Mackay, D. M. (1956) *in* Third London Symposium on Information Theory (edited by C. Cherry). London.
Matte-Bianco, I. (1959) *Int. J. Psycho-Anal.* **40**, 1.
Mayer-Gross, W., Slater, E. T. O., Roth, M. (1954) Clinical Psychiatry; p. 181. London.
Money-Kyrle, R. E. (1956) *Brit. J. Phil. Sci.* **7**, 86.
Ostow, M. (1957) *Arch. Neurol. Psychiat.* **77**, 79.
Pitts, W., McCulloch, W. S. (1947) *Bull. math. Biophys.* **9**, 127.
Polanyi, M. (1958) Personal Knowledge. London.
Richardson, M. (1957) *Observer*, Dec. 22.
Rickman, J. (1957) Selected Contributions to Psychoanalysis. London.
Ruesch, J., Bateson, G. (1951) Communication: the Social Matrix. New York.
Sawyer, W. W. (1955) Prelude to Mathematics; p. 12. Harmondsworth, Middlesex.
Shannon, C. E., Weaver, W. (1949) Mathematical Theory of Communication. Chicago, Ill.
Sluckin, W. (1958) *Sci. News*, **47**, 76.
Stanton, A. H., Schwarz, M. S. (1954) The Mental Hospital; p. 31. London.
Taylor, W. K. (1956) *in* Third London Symposium on Information Theory (edited by C. Cherry). London.
— (1958) *Brit. med. J.* ii, 967.
Thorpe, W. H. (1956a) Learning and Instinct in Animals; p. 103. London.
— (1956b) *ibid.* p. 9.
Turing, A. M. (1954) *Sci. News*, **31**, 7.
Uttley, A. M. (1955) *in* Automata Studies (edited by C. E. Shannon and J. McCarthy). Princeton.
Weiss, E. (1957) *Int. J. Psycho-Anal.* **38**, 209.

GUANETHIDINE

HYPOTENSIVE DRUG WITH PROLONGED ACTION

A. W. D. LEISHMAN
M.A., D.M. Oxon., F.R.C.P.
PHYSICIAN

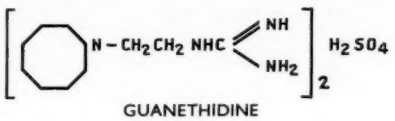
H. L. MATTHEWS
M.B. Manc., M.R.C.P.
SENIOR MEDICAL REGISTRAR

A. J. SMITH
M.A., B.M. Oxon., M.R.C.P.
MEDICAL REGISTRAR

ROYAL INFIRMARY, SHEFFIELD

DESPITE the development and improvement of ganglion-blocking drugs, the inescapable effects of parasympathetic blockade which appear with high dosage limit their usefulness as hypotensive agents, and the recent introduction of bretylium tosylate (' Darenthin ') (Boura et al. 1959), a hypotensive drug which selectively blocks peripheral sympathetic nerves, undoubtedly marks an important " break-through ".

Following quickly on this event, the discovery has been reported of another drug which, although chemically unrelated to darenthin, appears to lower blood-pressure similarly by inhibiting adrenergic-nerve action.



GUANETHIDINE

The hypotensive properties of the drug, 2-perhydroazocin-1′-ylethylguanidinium sulphate ('Ismelin', guanethidine) were first demonstrated by Maxwell et al. (1959) in unanæsthetised dogs with experimentally induced hypertension, when it was found that blood-pressure was much reduced by intravenous injection of 7·5–15 mg. of this compound per kg. body-weight. Although in normotensive dogs the effect on the diastolic pressure was slight, the drug inhibited the normal pressor response to carotid occlusion and antagonised the pressor effects of high doses of amphetamine.

In both dogs and cats relaxation of the nictitating membranes developed 6–12 hours after intravenous injection of the drug, and it was not possible to produce retraction of these membranes by stimulation of the preganglionic cervical sympathetic trunk, this effect persisting for 1–2 weeks. Except for a very transient period, no block in transmission across the superior cervical ganglion nor interference with conduction in preganglionic nerve-fibres could be demonstrated. But, while still unresponsive to nerve stimulation, the nictitating membrances were found to be abnormally sensitive to injected noradrenaline. From these data Maxwell et al. concluded that the drug "inhibits the release and/or distribution of transmitter substances from sympathetic nerve terminals".

Page and Dustan (1959) confirmed the hypotensive action of guanethidine given intravenously to hypertensive dogs; and in experiments lasting 6–9 weeks they observed in hypertensive dogs a pronounced and sustained fall of blood-pressure when the drug was given by mouth. They noted that, after the drug had been discontinued, several days elapsed before the blood-pressure started to return to its original level.

In pharmacological experiments on normal dogs they showed that the expected pressor response to amphetamine, ephedrine, or tyramine was usually reduced or abolished following intravenous injection of guanethidine, while the effects of noradrenaline, vasopressin, and hypertensin were often enhanced. They also found that, unlike ganglion-blocking agents, guanethidine did not reduce the pressor response to splanchnic nerve stimulation.

In general, therefore, there is no doubt that the actions of guanethidine so far studied in animals closely resemble those of bretylium tosylate, and that both drugs appear to act by selective blockade of the sympathetic nervous system. As yet, no information is available concerning the distribution, exact site of action, or rates of absorption and excretion of guanethidine.

Clinical trials of guanethidine in hypertensive patients have been reported from the United States by Page and Dustan (1959), Richardson and Wyso (1959), and Frohlich and Freis (1959). Page and Dustan gave guanethidine by mouth to 18 hypertensive patients for 2–10 weeks, in doses varying from 25 mg. on alternate days (1 patient) to 450 mg. daily, only 3 patients in the group receiving less than 75 mg. daily. In all their cases blood-pressure was reduced, the onset of the hypotensive effect being sometimes delayed for a week or more, and in 1 patient on intermittent treatment persisting for several days after the last dose.

Similar results were obtained in the other two trials, and all of these workers have drawn attention to the long-continued action of guanethidine. No toxic effects were detected, but side-effects were common, diarrhœa and severe postural hypotension apparently being the most troublesome.

Clinical Material

At present 25 hypertensive patients (10 men, 15 women) have been treated with guanethidine for 3–11 weeks. An additional patient who previously had symptoms suggesting caroticovertebral stenosis, died at home from a stroke after 2 weeks' treatment. Blood-pressure control in her case had been gradual and moderate and was unaccompanied by hypotensive symptoms. She had also been maintained on anticoagulant treatment.

Cases selected for the trial were of varying severity but included 1 patient (case 20) with malignant hypertension who had papillœdema which cleared during treatment. Apart from 1 case of hypertension secondary to polycystic kidneys, and at least 1 case of chronic pyelonephritis, the others were regarded as cases of primary hypertension. 1 patient (case 16) previously had undergone lumbodorsal sympathectomy, 14 had received ganglion-blocking drugs with or without reserpine, and 1 patient had been taking reserpine alone. All forms of treatment were discontinued before the start of the trial.

Method

Every patient was admitted to hospital for preliminary investigation and the early stages of treatment. In the first phase of the trial this usually occupied 3 weeks, but more recently patients treated with lower doses of the drug have been discharged to outpatient observation after 4–5 nights in hospital. To avoid the hypotensive effect of excessive rest the patients remained ambulant and activity was encouraged.

Investigations included chest X-ray, electrocardiography, urea clearance, urine concentration and dilution tests, urine microscopy and culture, routine hæmatological examination, erythrocyte-sedimentation rate, and estimation of serum-electrolytes. These occupied the first two days in hospital, during which the average level of pre-treatment blood-pressure was established. Blood-pressure was recorded four times daily in both lying and standing positions throughout each patient's stay in hospital.

Dosage

Guanethidine was supplied in 10 mg. tablets and was usually given by mouth in a single dose at 9.30 A.M. Division of the dose did not appear to offer any advantage.

With the single reported experience of Page and Dustan (1959) available for guidance at the time when this trial was

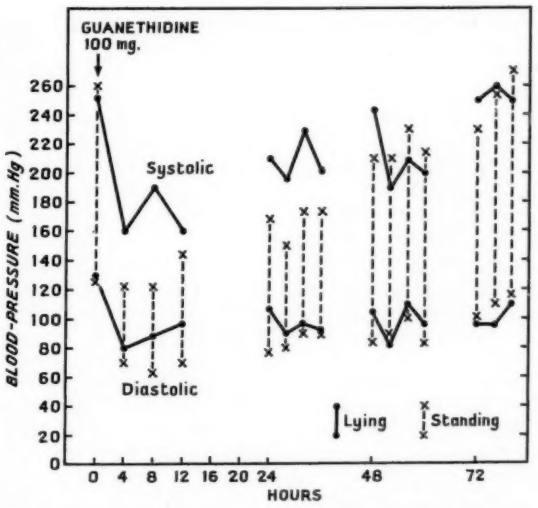


Fig. 1—Blood-pressure response to single dose of guanethidine in a hypertensive patient.

started, choice of a starting dose was inevitably somewhat arbitrary. Difficulty here was further increased by lack of knowledge of the rate of absorption and excretion of the drug; neither was it known whether a cumulative effect might be encountered, nor whether initial "loading" doses would be desirable.

The first patients treated therefore received 50–100 mg. guanethidine daily—a range of dosage well inside that adopted by Page and Dustan (1959) which, though unquestionably effective, had been accompanied by side-effects. Early in the trial, however, it became evident that individual sensitivity varied very greatly; and after a prostrating hypotensive response by 1 patient to a single dose of 100 mg. (fig. 1) patients were given an initial test dose of 50 mg. Later changes of dose were guided by blood-pressure response, but uncommonly were made at intervals of less than 2 days in view of the prolonged action of the drug and a possible cumulative effect.

With doses of this order, however, side-effects (described below) were soon encountered, and, since these became increasingly severe and in some cases alarming during the 2nd and 3rd weeks of treatment, a further revision of policy was necessary. The dose of all patients with severe side-effects was therefore reduced to 20 mg. daily, and new patients were given a test dose of 30 mg. followed either by 10 or 20 mg. daily in the succeeding week according to the hypotensive response to the test dose. Thereafter dosage was reviewed weekly in the outpatient department and where necessary was increased or decreased by not more than 10 mg. at each attendance until satisfactory blood-pressure readings were attained.

Hydrochlorothiazide (12·5 mg. twice daily) was given in addition to 6 of the patients receiving guanethidine.

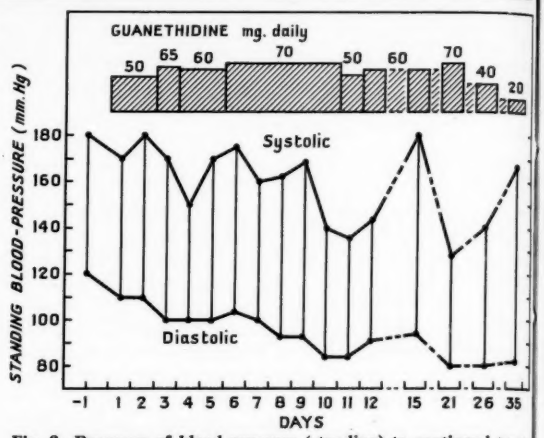


Fig. 2—Response of blood-pressure (standing) to continued treatment with guanethidine.

TABLE I—PROGRESS OF 19 HYPERTENSIVE PATIENTS TREATED WITH GUANETHIDINE

Case no.	Age (yr.)	Sex	Pre-treatment B.P.	Weeks treated	First week			Second week			Third week			Fourth week			Last week		
					Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects
1	55	F	300/150 248/144	10	50→100 →80→70 →80	220/120 164/100	Nil	70→80	232/110 160/100	Nil	80	230/122 186/112	H D	100	248/128 150/94	H D M	60	273/136 230/118	Nil
2	60	F	212/112 206/120	9	50→65 →60→70	180/96 162/98	Nil	70→50 →60	148/88 120/76	H D	60→70	160/90 128/80	D M+	40	138/70 140/80	D M	25	204/114 180/94	M
3	35	M	190/110 195/116	9	50→60 →100	140/95 130/94	Nil	100→80	162/94 140/80	D M	80	150/90 124/82	H D	80	160/98 140/88	D	50	168/88 160/88	Nil
4	30	F	188/106 200/126	9	50→60 →70	120/88 115/80	Nil	80→70	146/84 114/70	D	70→50	160/100 106/70	D M	50	154/92 136/88	D	30	178/98 150/92	Nil
5	55	M	230/120 190/118	9	50→60 →100	198/102 196/106	Nil	100	170/98 168/90	Nil	100	210/110 210/110	D M	100	190/96 190/96	Nil	50	230/130 230/132	Nil
6	38	M	190/120 200/130	9	50→60 →100	174/108 128/96	Nil	100	170/104 138/98	D	100	174/112 122/88	D H M	70	160/100 130/90	D M	50	190/108 160/104	Nil
7	54	M	250/144 230/144	8	100	190/128 206/128	Nil	100→130	210/130 210/126	D M+	150→0	212/120 198/118	Nil	20	220/130 220/130	Nil	50	238/132 218/118	H
8	48	F	254/104 300/130	8	100→50	230/92 220/88	D	50	240/100 160/90	D	50	210/94 150/80	M	30	236/100 166/90	Nil	50	250/92 190/88	H
9	56	M	230/130 230/130	8	100	200/112 188/94	H D	100→130 →150	170/96 138/76	H	150 →20	280/120 270/128	H D	40	270/130 240/120	H	60	230/110 180/98	H
10	72	F	250/128 260/130	8	100→0 →10→20	250/98 230/78	D+ H+	40	256/96 184/78	D+ H	40→0 →10	200/88 140/64	H+ D	10	258/88 128/56	D H+	10	226/130 220/108	H
11	62	F	210/122 220/128	8	50→80 →100→80	210/100 210/100	D+	80	230/108 190/96	D+	80	262/116 210/98	D+ H	50	240/122 206/100	D+	40	220/110 180/100	Nil
12	51	F	300/144 270/140	7	50→100 →140	240/136 230/120	H	140→150 →20	300/150 242/138	D H	40	290/140 242/120	M H	40	300/140 262/124	Nil	50	280/140 240/116	M
13	53	M	254/150 240/134	7	50→100 →80	130/78 128/70	H	80→20	198/120 182/105	H	20	250/130 230/112	H	30	250/128 228/112	H	50	230/120 190/100	H
14	61	F	200/124 210/130	7	50→60 →80→40	188/80 130/76	H D	20→10	290/130 200/126	D	20	260/130 210/120	D M	30	230/112 190/104	H	35	240/120 200/110	H
15	53	F	250/140 200/140	5	30→50 →20→10	220/110 148/96	H	10	250/130 230/126	Nil	20	240/130 180/110	H M	20	220/124 170/110	H+ M	10	260/132 216/118	Nil
16	42	M	240/130 230/120	3	30→10	200/130 160/120	Nil	20	200/130 164/120	Nil	..	..	..	..	..	..	30	218/122 160/112	Nil
17	57	F	220/116 200/116	3	30→20	240/120 210/110	Nil	30	240/102 168/84	Nil	..	..	..	..	..	..	30	240/110 190/96	H
18	60	F	210/114 205/130	3	30→20	230/120 220/122	Nil	30	236/112 210/108	H	..	..	..	..	..	..	35	248/100 220/100	Nil
19	59	M	220/110 180/120	3	30→20	256/120 182/118	Nil	20	200/120 200/110	Nil	..	..	..	..	..	..	30	260/114 178/98	Nil

Blood-pressure: first reading supine, second reading standing. H = hypotensive symptoms; D = diarrhœa; M = muscular symptoms.

TABLE II—PROGRESS OF 6 HYPERTENSIVE PATIENTS TREATED WITH GUANETHIDINE AND HYDROCHLOROTHIAZIDE

Case no.	Age (yr.)	Sex	Pre-treatment B.P.	Weeks treated	First week			Second week			Third week			Fourth week			Last week		
					Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects	Daily dose (mg.)	B.P.	Side-effects
20	69	F	300/142 300/140	11	20→50	274/128 272/126	H	100→80	218/98 174/92	H	60→50 →40→30	214/114 190/112	H D *	35→50 →60	235/100 215/98	H	30	260/118 200/100	H
21	58	M	210/130 220/135	6	50→100 →20	170/106 148/106	Nil	20	216/120 186/108	Nil	30	170/106 150/88	Nil	30	190/106 180/104	Nil	50	184/114 170/108	Nil
22	48	M	266/164 240/162	5	50→100 →20	240/150 200/130	Nil	20	276/160 240/142	Nil	30	268/144 224/130	Nil	..	..	..	40	248/140 204/118	Nil
23	51	F	270/144 260/154	5	50→100 →20	270/144 252/128	Nil	20→30	232/130 204/116	Nil	..	..	..	40	220/120 180/100	H	40	242/136 218/114	Nil
24	52	F	220/130 190/130	5	30→50 →20	166/100 138/88	Nil	20	210/120 180/130	Nil	30	220/120 190/118	Nil	40	200/120 180/110	Nil	50	230/130 194/116	Nil
25	62	F	208/134 210/130	5	30→50 →20	220/114 200/116	H	20	230/130 210/118	H	30	220/120 160/100	Nil	35	250/128 210/106	H+	25	240/128 198/108	Nil

Blood-pressure: first reading supine, second reading standing. H = hypotensive symptoms; D = diarrhœa; M = muscular symptoms; * = œdema.

Results

EFFECTS ON BLOOD-PRESSURE

The results are summarised in tables I and II.

If the level of the standing diastolic pressure is accepted as the criterion of hypotensive effect, the blood-pressure of 13 of the 19 patients treated with guanethidine alone (table I) can at present be regarded as satisfactorily controlled, and all but 1 of the remaining patients are showing some reduction of blood-pressure. Of the 6 patients who received hydrochlorothiazide in addition to guanethidine (table II) 5 are well controlled.

These results have confirmed that guanethidine by mouth is a potent hypotensive agent in man. Its hypotensive effect was predominantly postural, but some reduction in blood-pressure was usually evident in the lying position.

A fall of blood-pressure was commonly noted 4 hours after the drug was taken, its extent depending both on the patient's sensitivity and on the size of the dose. This transient effect at 4 hours usually continued throughout treatment but was superimposed on a gradual and progressive reduction in the average daily blood-pressure (fig. 2), and apart from this 4-hour effect the diastolic pressure showed little diurnal fluctuation.

On a constant effective daily dose the blood-pressure often fell progressively for about 7 days and then remained stable at the lower level unless the dose was changed. In 2 cases in which the drug was temporarily withdrawn the blood-pressure did not return to the pre-treatment level in less than 4 days.

COMPLICATIONS

Hypotensive

Symptoms due to postural hypotension were common. These varied from slight dizziness to incapacitating faintness and were notably more severe in patients who had received daily doses of guanethidine in excess of 60 mg. 2 patients with a previous history of transient attacks suggestive of cerebral ischæmia developed similar symptoms during a hypotensive phase, and 2 other patients complained of blurred vision during treatment. In contrast to the effect of recent lumbodorsal sympathectomy, hypotensive symptoms in many cases were provoked rather than relieved by walking exercise, and records of blood-pressure during exercise on a stationary bicycle confirmed that these symptoms are associated with a further fall in blood-pressure. A similar hypotensive response to exercise in patients treated with ganglion-blocking drugs was observed by Rønnov-Jessen (1953).

Symptoms due to postural hypotension, however severe, were immediately relieved by recumbency.

Side-effects

Diarrhœa.—This was the most constantly observed side-effect. In 2 cases it was severe with 8–10 fluid stools daily but without blood or mucus. In a further 12 patients there was mild diarrhœa. Its severity was closely related to the size of the dose, and diarrhœa often developed within 4 hours of the initial dose, thus coinciding with the first observed fall in blood-pressure. When the dose was reduced there was usually an improvement, and this symptom so far has not presented any problem to the patients whose treatment was started with smaller doses.

Myalgia and muscle weakness.—In the early stages of the trial, when large doses of guanethidine were commonly given, there were frequent complaints of excessive fatigability, muscle aching with subjective motor weakness, and general lack of well-being. These symptoms were at first very disabling but improved when doses were reduced. They did not appear to be invariably associated with hypotension.

Bradycardia.—Patients treated with guanethidine consistently developed bradycardia, but this caused no subjective symptoms and the pulse-rate accelerated normally on exercise.

Sexual function.—Male patients under treatment have not experienced any loss of libido or potency but failure of ejaculation has been noted.

Other side-effects.—During treatment with guanethidine 1 patient with incipient heart-failure developed dependent œdema, ascites, and increased jugular venous pressure which were largely relieved by hydrochlorothiazide. A further 4 patients without visible œdema showed unexplained gain of weight of approximately 2 kg. No disturbance of serum-electrolyte levels was observed in any of these patients, but sodium and water balance have not been studied. Minor effects occasionally encountered included smarting of the eyes and blurring of vision unrelated to hypotensive effect. In 1 case the visual disturbance was associated with marked pupillary constriction.

Toxic Effects

No appreciable changes in hæmoglobin levels or white-blood-cell counts were noted during treatment, but in

2 patients the erythrocyte-sedimention rate increased without obvious explanation.

In 7 patients the blood-urea level rose during treatment by 5–48 mg. per 100 ml.; in 5 of the 7 cases the level later returned to normal.

Discussion and Conclusions

The capacity of guanethidine to reduce the blood-pressure of hypertensive patients without symptoms of parasympathetic blockade is consistent with a mechanism of selective sympathetic-nerve inhibition; and the evidence both of animal experiment and of clinical trial supports the view that in this respect the actions of bretylium tosylate and guanethidine are similar. Apparently, too, these drugs largely share the same side-effects, for almost all the complications noted during guanethidine treatment appear to have been observed also among patients who were treated with bretylium tosylate (Smirk and Hodge 1959).

Guanethidine, however, differs strikingly from bretylium tosylate in the greater duration of its hypotensive effect. This could have advantages, for a drug which lowers blood-pressure by graduated stages without diurnal fluctuation approaches more closely to the ideal requirements of hypotensive therapy. This characteristic suggests that treatment with guanethidine could with certain precautions (see below) be conducted entirely on an out-patient basis, since, with diastolic pressure remaining stable, dose adjustments can be based on blood-pressure recorded at any hour regardless of the time at which the last dose was taken.

On the other hand our early experience with doses which were clearly too high showed that guanethidine is not a harmless drug, and if immunity from serious side-effects is to be guaranteed the limits of tolerable dosage will have to be strictly defined.

Tolerance to the drug appears to be related not only to the size of the individual dose but also to the rate at which dosage is increased and the extent of each increment. Thus, although the first results of this trial suggested that side-effects must be expected with doses of the order of 60 mg. daily, it seems possible in the light of later experience that higher doses, should they be necessary, may prove tolerable provided they are approached by slow stages.

A cumulative effect might have been responsible for the special prevalence of side-effects during the 2nd and 3rd weeks of treatment with relatively large doses of guanethidine. There has been no indication of this with smaller doses, and blood-pressure has usually responded as expected to the weekly alteration of dose.

The trial has shown that any dosage scheme, if it is to be safe, must identify the occasional patient who is hypersensitive to the drug's action. The blood-pressure of one patient, for example, is at present well controlled on a daily dose of 10 mg. guanethidine, and Page and Dustan (1959), who generally employed large doses, also reported a single case which did not require more than 12·5 mg. guanethidine daily.

The present policy of determining the response of each patient to a single test dose of intermediate size (30 mg.) before initiating daily treatment with doses of 10 or 20 mg. guanethidine appears, therefore, to be reasonable.

So far no patient who has started treatment in this manner and subsequently has been restricted to dose increments of not more than 10 mg. at weekly intervals has suffered serious side-effects.

At present the majority of the patients whose blood-pressures are satisfactorily controlled require 30–60 mg. guanethidine daily. A few patients have appeared to develop some resistance to the drug, and it is possible that ultimately their requirements may be rather greater.

The addition of hydrochlorothiazide has not so far modified the response to guanethidine.

These early observations have shown that guanethidine is an effective hypotensive drug which is simple to administer and, with suitable precautions, can be employed in the treatment of hypertensive patients. Its usefulness may ultimately depend on the size of the maintenance dose required by the majority of hypertensive patients. If, as at present seems likely, in most cases this lies below the level at which troublesome side-effects are encountered, guanethidine may prove to be a drug of considerable potentiality.

Summary

25 hypertensive patients have been treated with 2-perhydroazocin-1′-ylethylguanidinium sulphate (' Ismelin', guanethidine) by mouth for 3–11 weeks. 6 of these patients received hydrochlorothiazide in addition.

The blood-pressure fell in all but 1 of the patients. The hypotensive effect is long-continued and predominantly postural. In 18 cases the blood-pressure is now considered to be satisfactorily controlled.

Symptoms of severe hypotension as well as side-effects were common early in the trial, when guanethidine was often given in doses exceeding 60 mg. daily, but recent experience has suggested that dosage of this order will seldom be required.

Side-effects ceased to be troublesome when treatment was started with 10 or 20 mg. guanethidine daily, the dose being subsequently increased by not more than 10 mg. at weekly intervals.

The hypotensive action of guanethidine appears to be due to selective blockade of the sympathetic nervous system. In this respect its action resembles that of bretylium tosylate, although chemically the two drugs are unrelated.

Guanethidine is an effective hypotensive drug which reduces blood-pressure by progressive stages. It is easy to administer, and the trial has shown that, with suitable precautions, it can be employed in the treatment of hypertensive patients.

We are indebted to Dr. C. D. Falconer, medical adviser to Ciba Laboratories Ltd., for supplies of guanethidine and for helpful cooperation; and to Dr. B. J. Porter for assistance in this trial.

REFERENCES

Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. (1959) *Lancet*, ii, 17.
Frohlich, E. D., Freis, E. D. (1959) *Med. Ann. D.C.* **28**, 419.
Maxwell, R. A., Mull, R. P., Plummer, A. J. (1959) *Experientia*, **15**, 267.
Page, I. H., Dustan, H. P. (1959) *J. Amer. med. Ass.* **170**, 1265.
Richardson, D. W., Wyso, E. M. (1959) *Virginia med. (Semi-) Mon.* **86**, 377.
Rønnov-Jessen, V. (1953) *Lancet*, ii, 706.
Smirk, F. H., Hodge, J. V. (1959) *ibid.* ii, 673.

". . . Could man evolve radically, or be made to evolve radically, in future? . . . The answer, to be delivered with every inflection of impatience, is yes indeed. The necessary conditions are satisfied: a luxuriance of inborn diversity, a system of mating that maintains it, and an unspecialised structure as the zoologist uses that word, a structure which does not in itself commit human beings to any one way of life. From the point of view of genetical evolution, human beings have retained an amateur status."—Prof. P. B. MEDAWAR, *Listener*, Nov. 26, 1959, p. 921.

SERUM-BILE-ACID LEVELS IN LIVER DISEASE

E. C. OSBORN
B.Sc. App., Queensland
RESEARCH ASSISTANT

I. D. P. WOOTTON
M.B. Cantab., Ph.D. Lond., F.R.I.C.
SENIOR LECTURER

L. C. DA SILVA
M.D. São Paulo
BRITISH COUNCIL SCHOLAR

SHEILA SHERLOCK *
M.D. Edin., F.R.C.P., F.R.C.P.E.
LATE PHYSICIAN AND LECTURER

From the Departments of Chemical Pathology and Medicine, Postgraduate Medical School, London, W.12

IN human bile, the amount of the trihydroxy acid (cholic acid) roughly equals the sum of the two dihydroxy acids (chenodeoxycholic acid and deoxycholic acid) (Wootton and Wiggins 1953). Investigation of the metabolism of these substances in the presence of liver disease has been delayed because of the undoubted difficulties in their accurate analysis, especially in serum. Utilisation of the techniques of counter-current distribution, paper-chromatography, and sulphuric-acid fluorescence have opened the way to measurement, not only of the total-bile-acid level in serum, but also of the changes in the constituent main acid types and particularly in the ratio of trihydroxy to dihydroxy acids.

It has been suggested that the intolerable pruritus experienced by some patients with obstructive forms of jaundice is related to the retention of bile salts in the blood. The relation between this symptom and the serum-bile-acid values has therefore been investigated. This symptom can be relieved by sublingual methyltestosterone (Lloyd-Thomas and Sherlock 1952); and norethandrolone ('Nilevar') has been shown to be equally effective (Sherlock 1958). The effect of this treatment on the serum-bile-acid values has therefore been noted.

* Present address: Royal Free Hospital School of Medicine, London, W.C.1.

Corticosteroid drugs are being increasingly used in the treatment of some types of virus hepatitis, in active cirrhosis, and occasionally in the diagnosis of jaundice. An opportunity has been taken of studying the changes in serum-bile-acid levels when patients receive this treatment.

Patients Studied

51 patients were studied (tables I-IV). 6 patients had acute obstruction to the common bileduct with jaundice of less than two months' duration. The diagnosis in every instance was confirmed by laparotomy or necropsy. 12 patients had chronic obstructive jaundice of more than two months' duration. 2 patients had secondary biliary cirrhosis following a traumatic stricture of the common bileduct; and the other 10 had primary biliary cirrhosis, the diagnosis being cofirmed by laparotomy, needle hepatic biopsy, or necropsy.

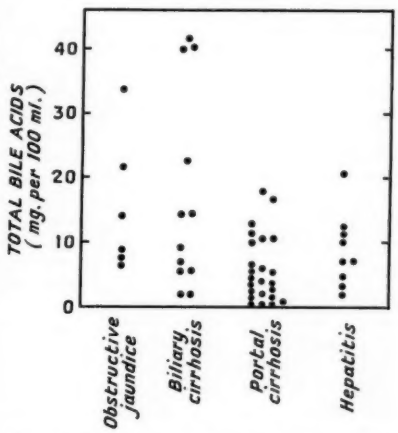


Fig. 1—Serum-total-bile-acid levels in the patients studied.

9 patients had acute virus hepatitis, 3 of serum and 6 of acute infective type.

Laennec's (portal or postnecrotic) cirrhosis was diagnosed in 24 patients. In 3 there was an antecedent history of acute hepatitis, and 5 were alcoholics. 9 were of the "juvenile" type showing jaundice and high serum-γ-globulin values at some stage of their illness. There were no obvious ætiological factors in the other 7. The diagnosis was supported in 22 instances by aspiration needle biopsy of the liver or by necropsy.

TABLE I—FINDINGS IN ACUTE OBSTRUCTIVE JAUNDICE

Case no.	Sex	Age (yr.)	Diagnosis	Pruritus	Duration (weeks)	Serum-bile-acids (mg. per 100 ml.)				Serum				
						Trihydroxy	Dihydroxy	Total	Trihydroxy / Dihydroxy	Bilirubin (mg. per 100 ml.)	Phosphatase (units per 100 ml.)	Cholesterol (mg. per 100 ml.)	Albumin (g. per 100 ml.)	Globulin (g. per 100 ml.)
1	M	54	Cancer of pancreas..	+	4	18·7	14·8	33·5	1·3	10·0	34	390	3·3	3·3
2	M	56	Cancer of bileducts	+	5	13·3	8·0	21·5	1·7	13·5	182	276	2·7	3·3
3	F	42	Cancer of bileducts	−	7	10·8	3·0	13·8	3·6	14·6	65	293	3·4	3·2
4	M	63	Cancer of pancreas..	−	3	10·2	6·6	18·8	1·6	12·8	76	286	3·0	4·7
5	F	50	Primary liver cancer	+	4	4·2	3·5	7·7	1·2	3·6	57	..	1·9	4·7
6	F	62	Gallstone	−	6	3·3	3·7	7·0	0·9	10·8	72	..	2·3	2·3

TABLE II—FINDINGS IN BILIARY CIRRHOSIS (ALL CASES EXCEPT 7 AND 18 OF PRIMARY TYPE)

Case no.	Sex	Age (yr.)	Duration (mos.)	Pruritus	Serum-bile-acids (mg. per 100 ml.)				Serum					Notes
					Trihydroxy	Dihydroxy	Total	Trihydroxy / Dihydroxy	Bilirubin (mg. per 100 ml.)	Phosphatase (units per 100 ml.)	Cholesterol (mg. per 100 ml.)	Albumin (g. per 100 ml.)	Globulin (g. per 100 ml.)	
7	F	58	36	−	1·5	3·7	5·2	0·4	2·6	68	..	..	..	Stricture of bileduct
8	F	45	37	+	12·8	10·0	22·8	1·3	6·9	68	365	3·6	3·9	..
9	M	29	36	+	1·8	0·4	2·2	..	6·0	..	266	4·1	3·6	..
10	F	40	..	+	7·3	7·1	14·4	1·0	3·1	101	293	3·2	4·5	..
11	F	47	48	+	4·0	1·6	5·6	2·5	1·8	45	280	4·6	3·4	Died liver failure
12	M	48	24	+	9·6	4·9	14·5	2·0	4·0	47	195	3·3	3·6	..
13	F	53	36	+	3·3	3·6	6·9	0·9	3·3	48	250	4·0	3·3	..
14	F	46	..	+	7·5	1·5	9·0	5·0	2·8	48	290	4·2	3·6	Died postoperatively
15	F	57	24	+	34·2	7·6	41·8	4·5	18·6	72	920	3·2	4·6	Died liver failure
16	M	52	60	+	19·2	20·8	40·0	0·9	15·7	175	780	3·2	4·6	..
17	F	52	120	+	0·9	1·4	2·3	..	1·6	92	480	4·5	3·5	..
18	F	73	10	+	14·2	11·8	26·0	..	12·4	96	1360	3·6	3·0	Stricture of bileduct; died postoperatively

Methods

Pruritus was considered to be present if the patient spontaneously complained of it, scratch marks were present on the skin, and relief was demanded by the patient. 6 patients received norethrandrolone (30 mg. daily), and the effect on pruritus and on serum-bile-acid levels was noted.

In 5 patients the effect of prednisone or triamcinolone on serum-bile-acid values was determined.

Biochemical

The total serum-bile-acid level and the proportion of the trihydroxy and dihydroxy components were determined by the method of Turner et al. (1959), which comprises six stages: (1) extraction by the method of Josephson (1935); (2) counter-current distribution; (3) alkaline hydrolysis of the conjugates; (4) preparation of the methyl esters; (5) paper chromatography of the esters (the two "spots" representing the trihydroxy and dihydroxy acids are extracted); (6) measurement of fluorescence in concentrated sulphuric acid (Turner et al. 1957).

Serum total bilirubin, alkaline phosphatase, cholesterol, albumin, globulin, thymol turbidity, and zinc-sulphate turbidity values were determined by standard procedures (King and Wootton 1956).

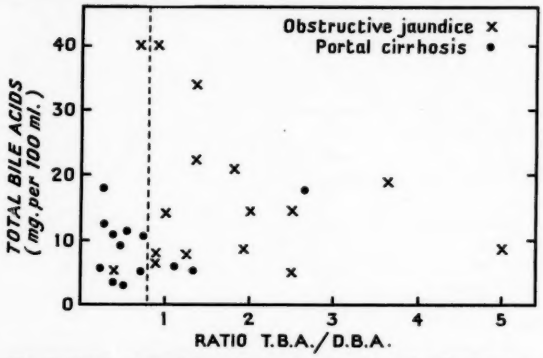


Fig. 2—Total serum-bile-acid level and ratio of trihydroxy to dihydroxy bile acids in obstructive jaundice and portal cirrhosis.

Results

Obstructive Jaundice

With 2 exceptions (cases 9 and 17) the total serum-bile-acid levels were raised more than 4 mg. per 100 ml. (fig. 1), the increase affecting both the trihydroxy and the dihydroxy acids (tables I and II).

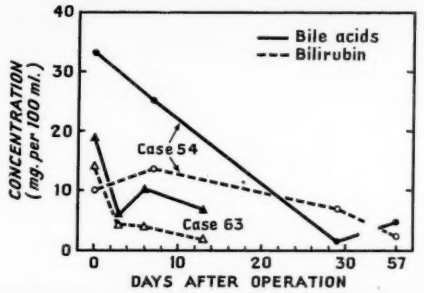


Fig. 3—Effect of cholecystenterostomy on serum bile-acid and bilirubin levels in 2 cases (cases 1 and 4, table I) of carcinoma of the head of the pancreas.

In the acute group, in every instance the ratio between trihydroxy and dihydroxy bile acids exceeded 0·8 (table I, fig. 2). In 2 patients with carcinoma of the head of the pancreas, the biliary obstruction was relieved by cholecystenterostomy and the serum-bile-acid values fell slowly towards normal (fig. 3).

In the chronic group, the patients with primary biliary cirrhosis showed ratios which exceeded 0·8 (table II, fig. 2). 3 of these patients died during the subsequent year, but in no instance could the ratio have been used to predict the fatal outcome. Of the 2 patients with secondary biliary cirrhosis, 1 (case 7) showed a low ratio of trihydroxy to dihydroxy acids.

There was a correlation between the serum-bilirubin and the total serum-bile-acid level ($r = 0{\cdot}71$) (fig. 4). Each milligramme of bilirubin retained corresponded to a rise of bile acid of $1^2/_3$ mg.

Portal Cirrhosis

Values were very variable (table III). Of the 24 patients 11 had levels raised less than 4 mg. (fig. 1). In general these were the less seriously ill patients with serum-bilirubin values of 1 mg. per 100 ml. or less, but there were notable exceptions.

Case 28, a widow of 52, a longstanding alcoholic, was in the terminal stages of cirrhosis with deep jaundice, gross ascites, and hepatic precoma. Serum-bile-acid levels were extremely low, the trihydroxy acids being 1·1 and the dihydroxy acid level 0·6 mg. per 100 ml. During the subsequent nine days the general condition worsened and the patient passed into deep coma. The serum-bilirubin level rose from 20·4 to

TABLE III—FINDINGS IN LAENNEC'S (PORTAL OR POST-NECROTIC) CIRRHOSIS

Case no.	Sex	Age (yr.)	Serum-bile-salts (mg. per 100 ml.)				Serum				Notes
			Trihydroxy	Dihydroxy	Total	Trihydroxy Dihydroxy	Bilirubin (mg. per 100 ml.)	Phosphatase (units per 100 ml.)	Albumin (g. per 100 ml.)	Globulin (g. per 100 ml.)	
28	F	52	1·1	0·6	1·7	..	20·4	22	2·1	4·7	Alcoholic; died hepatic coma
29	F	14	4·1	7·5	11·5	0·5	11·8	15	3·0	5·3	Pruritus
30	M	31	2·9	14·9	17·8	0·2	7·0	29	2·7	6·6	..
31	M	59	2·1	0·5	2·6	..	3·7	59	2·3	6·2	..
32	M	32	3·3	7·9	11·2	0·4	3·3	31	3·4	4·1	Pruritus; died
33	M	12	3·4	3·0	6·4	1·1	2·9	29	3·6	5·0	..
34	M	24	4·7	6·2	10·9	0·8	2·3	38	2·8	5·9	..
35	M	43	1·6	3·2	4·8	0·5	2·0	16	2·4	3·2	Posthepatic
36	M	19	1·0	4·8	5·8	0·2	1·8	9	2·5	5·2	Died septicæmia
37	M	15	0·8	1·0	1·8	..	1·6	20	3·0	3·6	..
38	M	37	3·0	9·4	12·4	0·3	1·3	14	3·8	2·8	Posthepatitic
39	M	33	3·0	2·4	5·4	1·3	0·9	61	4·0	4·0	..
40	F	50	2·3	2·9	5·2	0·8	1·0	11	2·1	2·3	..
41	F	48	3·2	0·6	3·8	..	1·0	50	3·2	4·2	..
42	M	47	1·1	0·6	1·7	..	1·0	26	2·7	4·8	Alcoholic; died hepatic coma
43	M	43	2·1	1·5	3·6	..	0·8	11	1·5	3·6	Died hepatic coma
44	F	50	0·5	..	0·5	..	0·7	8	2·9	4·6	Alcoholic
45	M	50	1·1	3·0	4·1	0·4	0·6	13	2·9	5·5	Died hepatic coma
46	F	51	..	0·2	0·2	..	0·6	15	3·9	3·0	..
47	M	41	0·8	..	0·8	..	0·6	8	3·1	4·2	Alcoholic
48	F	17	0·2	0·3	0·5	..	0·4	9	3·7	4·0	..
49	F	52	1·8	1·3	3·1	..	0·3	10	3·6	3·3	Alcoholic
50	F	14	2·8	7·6	10·4	..	21·4	14	3·1	5·5	..
51	F	17	12·6	4·8	17·4	..	11·0	13	3·1	5·6	Pruritus

37·2 mg. per 100 ml., and the trihydroxy bile acids rose to 4·8 mg. and the dihydroxy bile acids to 7·3 mg. per 100 ml.

In 13 of the 23 patients the serum-bile-acid level was raised more than 4 mg. per 100 ml. There was a correlation with the serum-bilirubin level. The ratio of trihydroxy to dihydroxy bile acids was usually low, exceeding 0·8 in only 3 of the 13 patients (fig. 2).

The patients in the "juvenile" group with high serum-γ-globulin values (cases 29, 30, 33, 34, 36, 37, 48, 50, and 51) showed, with 1 exception (case 48, who had received prednisone therapy for two years), raised bile-acid levels; the ratio of trihydroxy to dihydroxy acids was very variable.

Of the 23 patients 6 died during the subsequent year. The prognosis could not be closely associated with the total bile-acid level or with the ratio of trihydroxy to dihydroxy acids.

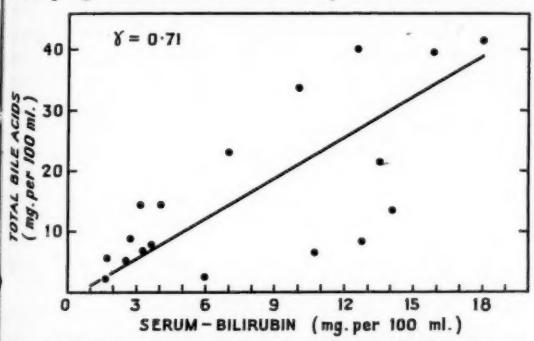


Fig. 4—Relation of serum-bile-acid to serum-bilirubin levels in 18 cases of obstructive jaundice.

There was a statistically significant difference ($P < 0·01$) between the high ratios in primary biliary cirrhosis and the low ratios found in Laennec's cirrhosis (fig. 2).

Virus Hepatitis

The total serum-bile-acid level was very variable (usually being raised and showing a correlation with the total serum-bilirubin value [table IV, fig. 1]). The ratio was usually above 0·7. Even the most severely affected patients showed raised serum-bile-acid levels.

Case 20, a girl aged 8 years, had ten days previously become jaundiced with malaise and pale stools. On the day before admission she became restless and disoriented and overnight passed into deep coma. The serum-bilirubin value was 16·2 mg. per 100 ml., and the serum-trihydroxy-bile-acids 5·3 mg. and dihydroxy-bile-acids 6·7 mg. per 100 ml. She died the next day. Necropsy showed the features of fulminant hepatitis.

In 3 instances analysis of serial samples showed that recovery from the hepatitis was followed by return of the bile acids towards normal.

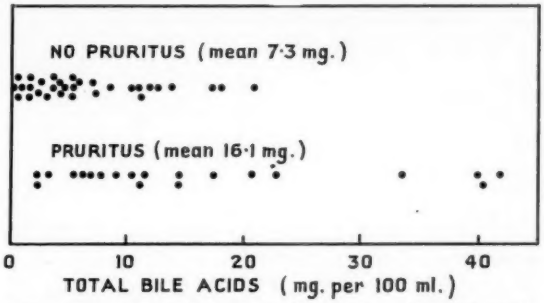


Fig. 5—Serum-bile-acid levels in 51 patients with jaundice: 31 without pruritus and 20 with pruritus.

Relation to Pruritus

This symptom was recorded in 20 of the 51 patients; 3 of these had acute obstructive jaundice, 11 chronic obstructive jaundice, 3 Laennec's cirrhosis, and 3 acute virus hepatitis. The mean total serum-bile-acid level was 16·1 mg. per 100 ml., compared with 7·3 mg. per 100 ml. for the patients without pruritus; and this difference is statistically significant ($P < 0·01$) (fig. 5).

There was, however, a good deal of overlap; in particular, 5 of the 20 patients who had pruritus showed total serum-bile-acid levels of less than 7 mg. per 100 ml., whereas 11 of 31 patients who did not have pruritus had bile-acid values greater than 7 mg. per 100 ml. There was no particular correlation of pruritus with the individual values for trihydroxy and dihydroxy acids.

The association of pruritus with low bile-acid values was, with the exception of 1 patient with hepatitis, recorded only in those with long-continued obstructive jaundice.

TABLE V—OBSTRUCTIVE JAUNDICE WITH PRURITUS: THE EFFECT OF NORETHANDROLONE (30 MG. DAILY) ON SERUM BILIRUBIN AND BILE-ACID LEVELS (IN EVERY INSTANCE THE PRURITUS WAS RELIEVED)

Case no.	Duration of therapy (days)	Serum-bilirubin (mg. per 100ml.)	Serum-bile-acids (mg. per 100 ml.)			
			Trihydroxy	Dihydroxy	Total	Ratio
2	0	13·5	13·3	8·0	21·3	1·7
	3	18·0	9·3	7·0	16·3	1·3
	7	15·0	6·9	10·0	16·9	0·7
13	0	3·3	3·3	3·6	6·9	0·9
	7	5·1	5·3	2·4	7·7	2·2
	13	7·2	3·8	2·8	6·6	1·4
9	0	5·3	4·2	2·9	7·1	1·4
	24	8·4	4·5	1·9	6·4	2·4
15	0	12·7	13·3	3·2	16·5	4·2
	21	18·6	34·2	7·6	41·8	4·5
5	0	3·6	4·2	3·5	7·7	1·2
	22	4·7	6·9	11·8	18·7	0·6
18	0	24·2	15·4	6·0	21·4	2·6
	6	25·7	25·1	25·8	50·9	1·0

TABLE IV—FINDINGS IN VIRUS HEPATITIS

Case no.	Sex	Age (yr.)	Duration (days)	Pruritus	Serum-bile-salts (mg. per 100 ml.)				Serum					Notes
					Trihydroxy	Dihydroxy	Total	Trihydroxy / Dihydroxy	Bilirubin (mg. per 100 ml.)	Phosphatase (units per 100 ml.)	Cholesterol (mg. per 100 ml.)	Albumin (g. per 100 ml.)	Globulin (g. per 100 ml.)	
19	M	46	6	+	7·4	2·9	10·3	2·6	8·0	18	..	3·1	3·8	Serum hepatitis
20	F	8	10	−	5·3	6·7	12·0	0·8	16·2	39	..	3·8	3·1	Died hepatic coma
21	M	40	7	−	5·6	5·6	11·2	1·0	16·0	22	171	3·1	3·7	Serum hepatitis
22	F	45	14	−	13·2	7·6	20·8	1·7	2·9	31	362	3·6	3·2	..
23	F	44	21	−	1·0	1·4	2·4	..	2·5	18	..	4·0	4·0	..
24	F	26	35	+	5·9	1·3	7·2	4·5	2·2	29	..	4·2	3·8	..
25	F	18	4	−	1·1	3·3	4·4	0·3	1·7	11	206	3·6	3·0	Pregnant
26	M	42	9	−	3·2	4·0	7·2	0·8	1·2	16	..	4·0	3·2	..
27	M	42	42	+	3·2	0	3·2	..	..	..	..	..	..	Serum hepatitis; died renal failure

TABLE VI—EFFECT OF CORTICOSTEROID THERAPY

Case no.	Diagnosis	Therapy (daily)	Duration (days)	Serum-bilirubin (mg. per 100 ml.)	Serum-bile-acids (mg. per 100 ml.)			
					Trihydroxy	Dihydroxy	Total	Ratio
50	Laennec's cirrhosis	Triamcinolone 20 mg.	0	9·1	9·8	9·6	19·4	1·0
			2	6·3	2·3	6·5	8·8	0·4
			3	3·2	5·4	9·0	14·4	0·6
			8	1·5	0·9	3·4	4·3	0·3
30	Laennec's cirrhosis	Triamcinolone 20 mg.	0	9·0	12·9	14·9	19·8	0·2
			27	2·0	1·3	2·6	3·9	0·5
9	Primary biliary cirrhosis	Prednisone 40 mg.	0	6·0	1·8	0·4	2·2	..
			9	3·1	3·2	3·8	7·0	0·8
			24	5·3	4·2	2·9	7·1	1·4
3	Carcinoma of hepatic ducts	Prednisone 30 mg.	0	9·4	3·6	1·4	5·0	2·6
			6	14·6	10·3	3·0	13·8	3·6
24	Virus hepatitis	Prednisone 20 mg.	0	2·2	5·9	1·3	7·2	4·5
			7	0·9	0·3	0·8	1·1	..
			22	0·6	1·3	2·4	3·7	..

Norethandrolone was given to 6 of the patients with acute or chronic obstructive jaundice who had pruritus (table v). In every instance within three days the pruritus had diminished and within a week it had disappeared. The serum-bilirubin level always increased. Serum-bile-acid values showed variable changes; in 1 there was a fall, in 2 the values did not alter significantly, and in 3 there was a rise. The ratio between trihydroxy and dihydroxy acids fell in 3 instances, rose in 2, and was the same in 1. These changes occurring at a time when itching was relieved made it seem unlikely that bile-acid retention in the blood was responsible for the pruritus.

Effect of Corticosteroid Therapy (Table VI)

Corticosteroid therapy (prednisone or triamcinolone) was given to 2 patients (cases 50 and 30) with active cirrhosis of juvenile type, and this was followed by a fall in serum-bilirubin and serum-bile-acid levels.

Case 50, a girl of 14 with the juvenile type of cirrhosis, made an excellent clinical response to triamcinolone therapy. Pruritus was relieved. In eight days the serum-bilirubin level had dropped from 9·1 to 1·5 mg. per 100 ml. This was associated with a fall in the total bile-acid level but the ratio between trihydroxy and dihydroxy acids was lower than before treatment. This patient has been maintained on triamcinalone for the past eighteen months and remains well.

Case 30, a man of 30, also showed an excellent clinical response to triamcinolone therapy. The serum-bilirubin level fell and with it the total bile-acid value fell. The ratio between the bile acids continued to be below 0·8. This man has been maintained on triamcinolone therapy for the past eighteen months and remains well.

2 patients had biliary obstruction, in 1 acute and in the other chronic.

Case 3, a woman of 42, with carcinoma of the hepatic ducts, received prednisone therapy in the early stages when the diagnosis was in doubt. A six-day course was followed by a rise in serum-bilirubin level, and this favoured the diagnosis of biliary obstruction rather than hepatitis. The serum trihydroxy and dihydroxy bile-acid levels also rose.

Case 9, a man of 29, with primary biliary cirrhosis had previously undergone two laparotomies (with operative cholangiography) which had failed to reveal obstruction to the main branches of the biliary system. Prednisone was given for relief of intractable pruritus. A course of twenty-four days did not affect the itching, and jaundice was virtually unchanged; bile-acid levels rose.

The 5th patient had acute virus hepatitis with predominantly obstructive features (Shaldon and Sherlock 1957).

Case 24, a 26-year-old housewife, had been jaundiced with pruritus for five weeks, and prednisone was given to aid diagnosis. Serum-bilirubin levels fell rapidly, and this favoured the diagnosis of hepatitis. The pruritus was relieved and serum-total-bile-acid fell.

Discussion

The method used is believed to be specific for bile-acids in serum. It has considerable advantages over the older and less specific methods using Pettenkofer's reaction (Josephson 1935) or the phosphovanillin reaction (Chabrol et al. 1934) which are claimed to measure cholic acid only. It certainly has the advantage of estimating the trihydroxy and dihydroxy fractions separately. Somewhat similar, newer techniques (Mosbach et al. 1954, Rudman and Kendall 1957, Carey 1958) do not use counter-current separation of the bile acids, and fluorescence measurements are more sensitive than ultraviolet absorption. The six stages individually give a good recovery, but the loss is cumulative so that the final recovery is only about 30%. This difficulty has been partly allowed for by running a recovery experiment with each batch of serum analysed. The full method is necessarily time-consuming, and the technique is not applicable routinely. A shorter, less specific, method more generally applicable is being evolved (Osborn and Wootton 1959).

The total amount of bile acids in normal serum cannot be more than 1 or 2 mg. per 100 ml. At such low levels the absolute values are unreliable and the ratio of dihydroxy to trihydroxy bile acids is of little value unless the total level exceeds 4 mg. per 100 ml.

Owing to the overlap between the increases in total serum-bile-acid concentration in hepatocellular and obstructive jaundice, this estimation is of no practical diagnostic value. A similar conclusion was reached for blood-cholates estimated by the Josephson technique (Sherlock and Walshe 1948). In non-jaundiced patients with minor degrees of liver dysfunction no elevation of circulating bile acids could be demonstrated.

The finding of low ratios of trihydroxy to dihydroxy acids excludes acute obstructive jaundice. The reverse association was not true, for high ratios sometimes occurred in deeply jaundiced cirrhotic patients without biliary-tract obstruction and occasionally in patients with acute hepatitis. Carey (1958) also noted a low ratio in portal cirrhosis and a high one in obstructive jaundice. He found 1·0 to be a dividing-line between the two groups. We find a better division at 0·8. This might be accounted for by the different analytical methods. Carey regarded a low ratio as a bad prognostic sign. Chabrol and Cottet (1935) also believed that a progressive fall of blood-cholic (trihydroxy)-acid levels was a bad augury. This has not been true in the present work; for, although low values have been noted in severe cirrhosis, 5 patients with ratios of 0·5 or less survived for a year. The patient who died with fulminant hepatitis had a ratio of 0·8.

The mechanism of the lowered ratios in hepatocellular disease is obscure. Failure of a 7α-hydroxylating or 12α-hydroxylating enzyme system in the liver is possible. Alternatively, overloading of injured liver cells by dihydroxy acids absorbed from the intestine would result in a predominant increase of these acids in the blood, and changes in intestinal flora may also be important. Similarly the cessation of the enterohepatic circulation due to blockage of the bileducts would account for the predominant accumulation of trihydroxy acids in patients

with obstructive jaundice, since the formation of deoxycholic acid is inhibited (Ekdahl and Sjövall 1958).

The pruritus of obstructive jaundice has been attributed to retention of bile salts which irritate cutaneous nerve-endings. There is little reported evidence to substantiate this hypothesis.

Brulé and Cottet (1942) observed that some, but by no means all, with higher cholic acid values (estimated by the phospho-vanillin method) had pruritus; in 1 patient pruritus disappeared while the blood-bile-acid values quadrupled. Similar results were reported by Rowntree et al. (1927) and by Carey (1958). Slow injection of cholic acid has failed to induce itching (Brulé and Cottet 1942, Sherlock and Walshe 1948). Ahrens et al. (1950), however, noticed that crude bile-salt preparations given to some jaundiced subjects produced itching, and we have confirmed this.

Although higher total bile-acid values tend to be found in those with pruritus, there is too much overlap to make a causal relationship likely. A similar overlap is apparent when the ratio is compared with the presence or absence of pruritus.

Norethandrolone therapy relieves the pruritus of obstructive jaundice without a fall in either total serum-bile-acids or the trihydroxy or dihydroxy fractions. This suggests that retention of these acids is not responsible for the pruritus. The mechanism of the antipruritic action is unknown. The coincident rise in serum-bilirubin concentration suggests a hepatic effect. Norethandrolone can cause jaundice in some patients without liver disease (Kory et al. 1959). This is of intrahepatic cholestatic type (Schaffner et al. 1959) resembling that occasionally complicating methyltestosterone therapy. Both norethandrolone and methyltestosterone are 17-alkyl substituted compounds. Both cause impairment of the removal of bromsulphalein in normal subjects (Dowben 1958, Kory et al. 1959). Bromsulphalein is conjugated by the liver in similar fashion to bilirubin before it is excreted into the bile. The relation of these findings to the antipruritic action of norethandrolone is not known, and the effect of norethandrolone on the conjugation of bile salts in the liver has not been investigated. Although jaundice deepened the patients showed no other ill effects on hepatic function.

In all 5 patients given corticosteroid therapy, the serum-bile-acid values followed the serum-bilirubin levels. The mechanism of the changes in serum-bilirubin values after steroid therapy is not known; the association of these with blood-bile-acid suggests that this is not an isolated effect on serum-bilirubin metabolism.

Summary

Serum-bile-acids were fractionated in 51 patients with liver disease by a method involving counter-current separation, paper-chromatography, and sulphuric-acid fluorescence. This allowed measurement of trihydroxy (cholic) and combined dihydroxy (chenodeoxycholic and deoxycholic) bile acids.

Increased total serum-bile-acid levels were recorded in obstructive and hepatocellular jaundice. Knowledge of the total bile-acid level is of no diagnostic value.

The ratio of trihydroxy to dihydroxy bile acids was above 0·8 in 6 patients with acute biliary obstruction and in 10 patients with primary biliary cirrhosis. Of 24 patients with Laennec's cirrhosis 13 showed a raised total serum-bile-acid value, and in only 3 of these did the ratio exceed 0·8. The prognosis could not be associated with the total bile-acid value or the ratio between the trihydroxy and dihydroxy acids.

9 patients with acute virus hepatitis, including 1 with the fulminant form of the disease, showed raised serum-bile-acid values.

Patients with pruritus showed a higher mean total serum-bile-acid value than those without this symptom, but there was considerable overlap between individual values.

In 6 patients with obstructive jaundice, norethandrolone relieved pruritus within a week. Serum-bilirubin values increased. Serum-bile-acid values fell in 1 case, rose in 3, and were unchanged in 2. Bile-acid retention in the blood did not seem to be responsible for the pruritus.

Corticosteroid therapy was given to 6 jaundiced patients. The bile-acid values followed the serum-bilirubin levels.

We wish to thank the Ames Company for financial support in the early stages of this work, and G. D. Searle & Co. for gifts of norethandrolone.

REFERENCES

Ahrens, E. H., Jr., Payne, M. A., Kunkel, H. G., Eisenmenger, W. J., Blondheim, S. H. (1950) *Medicine*, **29**, 299.
Brulé, M., Cottet, J. (1942) *Pr. méd.* **50**, 369.
Carey, J. B., Jr. (1958) *J. clin. Invest.* **37**, 1494.
Chabrol, E., Charonnat, R., Cottet, J. (1934) *C.R. Soc. Biol., Paris*, **115**, 835.
— Cottet, J. (1935) *Bull. Soc. méd. Hôp. Paris*, March 29.
Dowben, R. M. (1958) *J. clin. Endocrin.* **18**, 1308.
Ekdahl, Per-H., Sjövall, J. (1958) *Acta chir. scand.* **114**, 439.
Josephson, B. (1935) *Biochem. J.* **29**, 1519.
King, E. J., Wootton, I. D. P. (1956) Micro-analysis in Medical Biochemistry. London.
Kory, R. C., Bradley, M. H., Watson, R. N., Callahan, R., Peters, B. J. (1959) *Amer. J. Med.* **26**, 243.
Lloyd-Thomas, H. G. L., Sherlock, S. (1952) *Brit. med. J.* ii, 1289.
Mosbach, E. H., Kalinsky, H. J., Halpern, E., Kendall, F. E. (1954) *Arch. Biochem.* **51**, 402.
Osborn, E. C., Wootton, I. D. P. (1959) Unpublished.
Rowntree, L. G., Greene, C. H., Aldrich, M. (1927) *J. clin. Invest.* **4**, 545.
Rudman, D., Kendall, F. E. (1957) *ibid.* **36**, 530.
Schaffner, F., Popper, H., Chesrow, E. (1959) *Amer. J. Med.* **26**, 249.
Shaldon, S., Sherlock, S. (1957) *Brit. med. J.* ii, 734.
Sherlock, S. (1958) Diseases of the Liver and Biliary System; p. 390. Oxford.
— Walshe, V. (1948) *Clin. Sci.* **6**, 223.
Turner, M. D., Osborn, E. C., Wootton, I. D. P. (1957) *Biochem. J.* **67**, 31P.
— — — (1959) Unpublished.
Wootton, I. D. P., Wiggins, H. S. (1953) *Biochem. J.* **55**, 292.

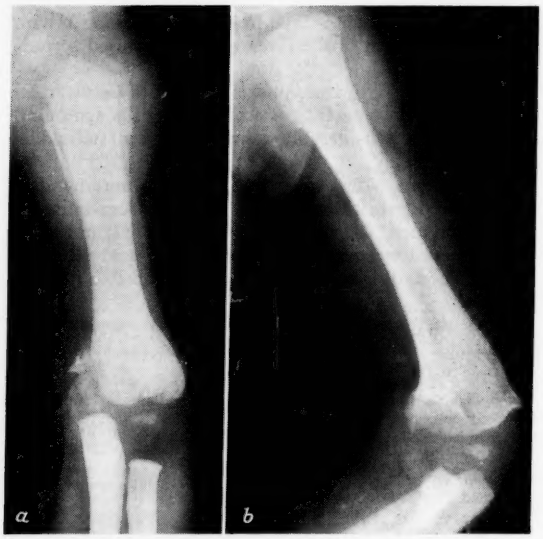
VACCINIAL OSTEOMYELITIS

W. D. ELLIOTT
M.B. Edin., M.R.C.P.E., D.C.H.
SENIOR PÆDIATRIC REGISTRAR,
ROYAL MANCHESTER CHILDREN'S HOSPITAL

VIRAL osteomyelitis is a recognised complication of smallpox. Cockshott and MacGregor (1958) reviewed the published reports of osteomyelitis variolosa and described the typical joint swellings, generally bilateral and symmetrical, which appear insidiously ten days to four weeks after the onset of smallpox in a growing child. They described the radiographic appearances of destructive changes in the metaphyseal ends of long bones, commonly extending to the epiphyses, and associated with extensive periosteal new-bone formation. They calculated that 2–5% of all children with smallpox had this complication, and cited reports of deformities following osteomyelitis variolosa with resulting destruction of epiphyseal cartilage.

Although smallpox is rare in this country, and few practitioners are likely to see variolar osteomyelitis, vaccination in infancy is practised widely, and vaccinial osteomyelitis might be expected.

Sewall (1949) reported the case of a girl who was vaccinated against smallpox when a year old. Two weeks later she developed mild pyrexia and non-tender swelling of the left forearm, and a month later a painless swelling appeared on her forehead. At the age of seventeen months she had a secondary anæmia and radiographic evidence of destructive changes



Vaccinial osteomyelitis: radiographs of left humerus and elbow-joint (*a*) six weeks after onset; (*b*) four months later.

involving the distal two-thirds of the left ulnar shaft, with extensive periosteal new-bone formation, and a porous area of the frontal bone, with a shadow suggesting a sequestrum. The vaccinia virus was found in a bone-biopsy specimen from the affected ulna. Sewall also mentioned another unpublished case in which the vaccinia virus was isolated.

Barbero et al. (1955) identified the virus in biopsy material from a metacarpal bone in a case of vaccinia gangrenosa in a five-year-old boy. Ten weeks after vaccination, which produced a progressively enlarging primary reaction with deep destructive necrosis of the skin and underlying tissues, he developed painless swelling of the dorsum of one hand. Radiographs a week later showed periosteal reaction over the mid-shaft of the 4th metacarpal bone.

Solito (1932) gave an account of an infant of nine months who developed painless pseudoparalysis of her left arm twelve days after vaccination in that arm, and recovered full movement within three weeks. Eighteen days after the pseudoparalysis started, radiographs of her left shoulder revealed destructive changes involving the metaphysis and epiphysis of the upper end of the humerus and the adjacent glenoid margin of the scapula, with periosteal new-bone formation in the humerus. The lesion resolved radiographically in four months.

Delano and Butler (1947) reported the case of an infant, vaccinated at the age of three months, who, ten days later, was severely ill, with pyrexia, stupor, increased intracranial pressure, and pseudoparalysis of the right arm. He had tender fusiform swellings over the distal half of both 5th metatarsals. His condition rapidly improved, but he relapsed nine days later with pyrexia, flaccidity of both arms, and a secondary anæmia. Radiographs revealed bilateral and symmetrical "ossifying periostitis" over the mid-shafts of the 5th metatarsals and clavicles, and periosteal involvement of the scapulæ and the upper ends of the humeri. The only unilateral lesion was an irregularity of outline at the lower end of one ulna. This case was regarded as an example of infantile cortical hyperostosis, probably of viral origin.

Brinkmann (1932) described the case of a girl of thirteen who had had a pyrexial illness, with pain and weakness in the left leg, following vaccination at one year. She was found later to have progressive shortening and deformity of her leg due to partial destruction of epiphyseal cartilage at both ends of the femur.

Kini and Kesavaswamy (1941), in an article on deformities resulting from smallpox, mentioned 2 cases of osteomyelitis of the humerus and 2 fatal cases of multiple osteomyelitis, all following vaccination against smallpox. These workers suggested their cases were due to spread of pyogenic organisms from infected vaccination sites, but they gave too little information to allow independent confirmation.

In this paper I record a further example of vaccinial osteomyelitis—the first to be reported in this country.

Case-report

A girl, born in September, 1957, was vaccinated in the left deltoid region early in February, 1958. Two weeks later she developed swelling, slight tenderness, and some limitation of movement of her left elbow. On Feb. 20 she was referred to an orthopædic outpatient clinic; her left humerus and elbow-joint showed no radiographic abnormality. The X-ray examination was repeated on March 10, five weeks after vaccination, and the humerus then showed periosteal new-bone formation over its lower third, with fragmentation of the lateral and medial condyles.

On April 1 her left elbow was still swollen, mainly laterally. The swelling was painless, but the infant was unwilling to use her left arm, and there was slight limitation of movement at the elbow-joint. A radiograph (see figure a) showed bone destruction at both ends of the humerus, with periosteal new-bone formation. The infant was pale and fretful; she had been losing weight for a few weeks, and feeding had been difficult.

The child was admitted to hospital on April 10, when she was seven months old. The findings were: weight 14 lb. 8 oz.; hæmoglobin 46%; red blood-cells 2·3 million per c.mm.; white blood-cells 9800 per c.mm. (polymorphonuclears 34%, lymphocytes 62%); Wassermann and Khan reactions negative; Mantoux test negative at 1/100; blood-culture sterile; gamma-globulin normal; serum-calcium 11·3 mg. per 100 ml.; serum-phosphate 6·4 mg. per 100 ml.; and serum-alkaline-phosphatase 26 King-Armstrong units. Radiographs continued to show destructive changes and periosteal new-bone formation at both ends of the humerus. No other bony abnormality was found.

Vaccinial osteomyelitis was diagnosed because of the history and the striking similarity in clinical and radiological findings to the cases reported previously. The anæmia was treated with iron intramuscularly, the child's appetite and general health improved, and she was discharged from hospital on May 11.

At an outpatient clinic on July 31, the child seemed well, active, and happy, and she weighed 16 lb. 9 oz. Her left elbow was no longer swollen, but it showed a cubitus-varus deformity, with limitation of flexion to 80° and of extension to 175°. A radiograph (see figure b) showed resolution of the osteomyelitis, but the distal end of the left humerus was deformed, indicating damage to the medial half of the epiphyseal cartilage. Six months later, in February, 1959, the findings were unchanged.

Discussion

Certain common features of vaccinial osteomyelitis become apparent from a study of the case-reports (see table).

CLINICAL FEATURES OF VACCINIAL OSTEOMYELITIS

Clinical features	Sewall (1949)	Solito (1932)	Delano and Butler (1947)	Brinkmann (1932)	Present case
Age when vaccinated	1 yr.	9 mos.	3 mos.	1 yr.	5 mos.
Onset of symptoms after vaccination	2 wk.	12 days	10 days	?	2 wk.
Pyrexia	+	−	+	+	?
Joint or bony swelling	+	−	+	?	+
Pseudoparalysis	−	+	+	+	+
Anæmia	+	?	+	?	+
Deformity	?	−	−	+	+
Bones involved	Radius, skull	Humerus, scapula	Metatarsals, clavicles, scapulæ, humeri, ulna	Femur	Humerus

The children affected were aged one year or less, presumably because vaccination is usually done in the first year of life. But since the very similar bony lesions of osteomyelitis variolosa are found at any age before fusion of the epiphyses, vaccinial osteomyelitis might also arise at any time during the period of growth.

The clinical features, starting ten days to two weeks after vaccination, included pyrexia, joint or bony swelling, and pseudoparalysis of a limb. Sudden weakness of a limb in infancy suggests a diagnosis of poliomyelitis, but a recent history of vaccination, and the radiographic changes characteristic of vaccinial osteomyelitis, would resolve any doubts.

Systemic upset varied from very mild to very severe, with secondary anæmia in three cases. Radiographically there were prominent destructive changes at the ends of the metaphyses of long bones, sometimes extending through epiphyseal cartilage to involve the epiphyses themselves, and being associated with extensive periosteal new-bone formation. In 2 cases the epiphyseal cartilage was permanently damaged, later causing shortening or deformity of a limb.

In 1 case (Delano and Butler 1947), which differed clinically in many respects from the others, the bony lesions were predominantly periosteal and symmetrical. Both clinically and radiographically Delano and Butler's diagnosis of infantile cortical hyperostosis seems to be justified, and I have included their case in this review with some reservations. In the other cases the clinical and radiographic picture is clearly not that of infantile cortical hyperostosis, nor do deformities from destruction of epiphyseal cartilage follow that disease. In the few examples of infantile cortical hyperostosis with deformities, these have been due to softening or destruction of the shafts of long bones (Caffey 1952). I included Delano and Butler's case because of the association of the infant's illness with vaccination, and because of an abnormality at the lower end of one ulna, which seemed to be the same destructive lesion as was encountered in the other cases. Moreover the case described by Barbero et al. (1955), though not strictly comparable with the others in view of the absence of the normal tissue response to primary vaccination, shows that the vaccinia virus can indeed cause the mid-shaft periosteal reaction seen in the metatarsals in Delano and Butler's case.

Summary

Vaccinial osteomyelitis is a very rare complication of vaccination against smallpox. The clinical and radiographic features in an affected infant are described and compared with those in 4 earlier cases.

Vaccinial osteomyelitis may arise insidiously, with little or no systemic upset, swelling of a joint or temporary weakness of a limb being the only indication of its presence. Hence it may remain undiagnosed in its early stages, but deformity may arise later from destruction of epiphyseal cartilage.

Vaccinial osteomyelitis should be considered in the differential diagnosis of limb weakness in the first or second year of life, and as a cause of limb shortening or deformity in early childhood.

I am indebted to Dr. G. M. Komrower for permission to publish this case; and to him and Prof. Wilfrid Gaisford for advice and encouragement.

REFERENCES

Barbero, G. J., Gray, A., Scott, T. F. McN., Kempe, C. H. (1955) *Pediatrics*, **16**, 609.
Brinkmann, E. (1932) *Z. Orthopäd. Chir.* **57**, 208.
Caffey, J. (1952) *Radiology*, **59**, 651.
Cockshott, P., MacGregor, M. (1958) *Quart. J. Med.* **27**, 639.
Delano, P. J., Butler, C. D. (1947) *Amer. J. Roentgenol.* **58**, 633
Kini, M. G., Kesavaswamy, P. (1941) *Antiseptic*, **38**, 169.
Sewall, S. (1949) *Bull. Hosp. Jt Dis.* **10**, 59.
Solito, M. (1932) *Quad. radiol.* **3**, 73.

HIRSUTISM AFTER ADRENALECTOMY

J. A. STRONG
M.B.E., B.A., M.B. Dubl., F.R.C.P.E., M.R.C.P.
SENIOR LECTURER IN MEDICINE

JOHN BRUCE
C.B.E., M.B. Edin., P.R.C.S.E.
REGIUS PROFESSOR OF CLINICAL SURGERY

C. W. A. FALCONER
M.B. Edin., F.R.C.S.E.
SURGEON, WESTERN GENERAL HOSPITAL

From the Departments for Endocrine and Metabolic Diseases and Clinical Surgery, Western General Hospital, and the University of Edinburgh

THE entity variously described as idiopathic hirsutism, simple hirsutism, and hirsutism of constitutional origin has long been recognised. It has been suggested that, when adrenocortical hyperfunction cannot be demonstrated, the cause may be abnormal sensitivity of the hair follicles to normal amounts of adrenal androgen (Wilkins 1957); but comprehensive studies by Kappas et al. (1956), Perloff et al. (1958) and Bush and Mahesh (1959) suggest that few, if any, cases of hirsutism are not caused by some disturbance of steroid hormone metabolism.

On the other hand, we have observed hirsutism exceeding that commonly seen in women at that time of life in two postmenopausal patients whose vigorous growth of facial hair continued after bilateral adrenalectomy and oophorectomy. This suggests that, in the postmenopausal patient at any rate, abnormal growth of hair on the face and beard area can occur when all the accepted sources of endogenous steroids have been removed. We have also observed a male patient in whom "sexual hair" grew after orchidectomy, adrenalectomy, and hypophysectomy: this also supports the idea that this type of hair may grow independently of the sex hormones.

Case-reports

Case 1.—A spinster, aged 60. Eleven months before the photographs shown in fig. 1 were taken this patient had undergone bilateral adrenalectomy and oophorectomy on account of metastatic disease in bone from a primary carcinoma of the breast. She remained well for approximately seven months after operation, when the bone pain returned. During the eleven months after operation, maintenance therapy consisted of cortisone acetate 12·5 mg. three times daily, and later 25 mg. twice daily.

(*a*) (*b*)

Fig. 1—Case 1. The beard and moustache area had been shaved on the day that photograph (*a*) was taken. Ten days later, without further treatment, (*b*) was taken.

Before adrenalectomy the patient received a short course of stilbœstrol. At that time she was slightly hirsute, but the hirsutism was more striking after adrenalectomy than before. The growth of facial hair eleven months after bilateral adrenalectomy and oophorectomy is illustrated in fig. 1.

Case 2.—A spinster, aged 57. Following the menopause at the age of 52, the patient noticed that facial hirsutism, pre-

(*a*) (*b*)

Fig. 2—Case 2. Photograph (*a*) was taken before bilateral adrenalectomy and oophorectomy. Shortly after these operations all facial hair was removed, but six weeks later hair growth had recurred to the extent shown in (*b*).

viously slight, increased considerably. When she came under observation for hormone treatment of widespread recurrent and metastatic mammary carcinoma, her appearance was as shown in fig. 2a.

Following a short course of treatment with stilbœstrol, and later with testosterone, both adrenals and ovaries were removed. A few days after operation her face was shaved, but within six weeks hair growth had recurred to the extent shown in fig. 2b. During this period she received cortisone acetate in doses varying between 37·5 and 75 mg. daily, and two injections each of 50 mg. of a suspension of desoxycorticosterone trimethylacetate ('Percorten', Ciba) at an interval of four weeks. Apart from the abnormal facial hair, no evidence of virilism was found.

Her condition deteriorated slowly and she died approximately eight months after operation. No residual adrenocortical tissue could be identified at necropsy.

Case 3.—A man, aged 73. At the age of 70 widespread metastases developed in bone from a mammary carcinoma removed two years earlier. After bilateral orchidectomy the patient's condition improved remarkably for about nine

(*a*) (*b*)

Fig. 3—Case 3. Beard growth after bilateral orchidectomy, adrenalectomy, and hypophysectomy. Ten days elapsed between (*a*) and (*b*).

months, and there was a further striking remission for about eighteen months after bilateral adrenalectomy. Sixteen months later his condition again began to deteriorate and he was submitted to hypophysectomy (Mr. F. J. Gillingham). Thereafter his bone disease appeared to improve, but his condition deteriorated slowly and he died five months later with very extensive metastatic disease of the liver. No residual adrenocortical tissue was identified at necropsy, though a rim of apparently viable pituitary tissue could still be identified in sections of the sella turcica, up to 2 mm. in thickness.

The photographs shown in fig. 3 were taken approximately three months after hypophysectomy; during this period he was receiving 50 mg. of cortisone daily.

Discussion

In these three patients facial hair grew vigorously after the removal of both gonads and adrenals. In two further female patients treated in the same way for mammary carcinoma, appreciable hirsutism was noted; and one of these (aged 66) stated that hair growth on her chin had only begun some months after adrenalectomy and oophorectomy.

Possibly the cortisone given as maintenance treatment was a sufficient source of androgenic steroid metabolites for hair growth to continue, but it is widely accepted that the amount of weak androgens likely to be formed in this way is small and therefore unlikely to cause appreciable virilisation. However, hirsutism in the postmenopausal female after adrenalectomy and oophorectomy, and beard growth in the male after orchidectomy, adrenalectomy, and hypophysectomy, may have one or more of several other explanations.

In the first place, the excisions may have been incomplete, so that hormone secretion was not abolished. Intensive study of hormone excretion after adrenalectomy has led us to conclude that the steroids excreted are probably not adrenocortical (Strong, Brown, Bruce, Douglas, Klopper, and Loraine 1956, Brown, Falconer, and Strong 1959). Secondly, apart from the fraction converted to weak androgens, the cortisone given as replacement therapy after adrenalectomy may suffice to maintain abnormal hair growth or to allow it to develop in the female, and to permit beard growth to continue in the male. Alternatively, hair growth of the type in question may not be "dependent" upon androgenic hormones for its continued growth. If this is so, it invites comparison with the failure of many cancers of the breast to regress after adrenalectomy.

The growth of coarse dark hair on the beard area and on the upper lip is usually accepted as a masculine secondary sex character that develops in response to a stimulus provided by the androgens secreted after puberty by the testes, and to a lesser extent by the adrenals. Hair growth of this type might therefore be said to be "dependent on" or "responsive to" circulating steroids with androgenic properties. Since it persisted or only developed after castration and adrenalectomy in the patients reported here, the condition may be said to have been no longer "hormone-dependent" or "hormone-responsive". Apparently in these patients the hair was not behaving as "sexual" hair, but had taken on the growth characteristics of the hair of the scalp.

We have now observed this type of hair growth in appreciable measure in 4 of a series of 61 patients treated for recurrent and metastatic mammary carcinoma by adrenalectomy and oophorectomy. If our experience truly reflects the incidence of hirsutism in these circumstances, it is remarkable that the phenomenon has not been more often reported.

Summary

In postmenopausal patients with metastatic breast cancer, excessive facial hair growth continued after bilateral adrenalectomy and oophorectomy.

In a man, aged 73, with metastatic mammary carcinoma, the beard continued to grow relatively vigorously after orchidectomy, adrenalectomy, and hypophysectomy.

REFERENCES

Brown, J. B., Falconer, C. W. A., Strong, J. A. (1959) *J. Endocrin.* **19,** 52.
Bush, I. E., Mahesh, V. B. (1959) *ibid.* **18,** 1.
Kappas, A., Pearson, O. H., West, C. D., Gallagher, T. F. (1956) *J. clin. Endocrin.* **16,** 517.
Perloff, W. H., Channick, B. J., Suplick, B., Carrington, E. R. (1958) *J. Amer. med. Ass.* **167,** 2041.
Strong, J. A., Brown, J. B., Bruce, J., Douglas, M., Klopper, A. I., Loraine, J. A. (1956) *Lancet*, ii, 955.
Wilkins, L. (1957) The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence; p. 338. Oxford.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

J. R. SIMPSON
M.B. Lond., M.R.C.P.
DERMATOLOGIST, ROYAL DEVON AND EXETER HOSPITAL, EXETER

PUBLISHED reports on vascular nævi show the need for clear definitions.

Nævus flammeus, port-wine stain, or capillary hæmangioma, present at birth and persisting throughout life, is characteristically a pink, red, or purple area of skin with a flat, smooth surface level with the surrounding skin. Its area does not increase relative to the growth of the patient, but in later life it may become darker and develop multiple small protuberances.

Cavernous hæmangioma or strawberry mark, on the other hand, which may be present at birth or may appear during the first 6 months of life, often grows considerably during the 1st year but disappears spontaneously by the age of 5–10 years. The surface of the lesion is always raised to some extent above the level of the surrounding skin. The abnormal vascular tissue may be confined to the dermis, may rarely be entirely hypodermal, or may lie partly in the dermis and partly in the hypodermis (the mixed form). The dermal element is usually sharply circumscribed and bright red in the early stages. The hypodermal element may be palpable only, but it often gives a faint blue tinge to the skin, and its limits are less easily defined.

In this paper I am concerned solely with cavernous hæmangiomata.

Duncan (1885) treated vascular nævi by electrolysis to his satisfaction towards the end of last century, but early in this century it became fashionable to irradiate them. The first recorded observations on untreated cases (Lister 1938) were prompted by the uncertainty of members of the Dermatological Section of the Royal Society of Medicine at a meeting in 1930, and by the scarcity of relevant information in the current textbooks. Lister showed clearly that most of these lesions resolved spontaneously within a few years. This has been confirmed since by several workers, including Brain and Calnan (1952), and Wallace (1953), and is accepted by most, if not all, British dermatologists. But in the United States particularly this concept seems to be gaining ground very slowly indeed, and, although some American dermatologists (Rhonchese 1953) are willing to spare small lesions on covered parts of the body, a nævus of this kind is rarely allowed to run its natural course. Moreover, even in the past 10 years radiotherapists and plastic surgeons have described techniques and stressed the indications for treatment.

TABLE I—AGE OF ONSET OF HÆMANGIOMATA IN 140 CHILDREN

Onset	No. of cases
Birth	39 (28%)
1st wk.	22 (16%)
2nd ,,	36 (26%)
3rd ,,	8 (6%)
4th ,,	17 (12%)
2nd mo.	9 (6%)
3rd ,,	3 (2%)
4th ,,	4 (3%)
6th ,,	2 (1%)

I here present more detailed information on the behaviour of cavernous hæmangiomata, and stress the advantages of expectant treatment.

The Series

140 children presented a total of 170 nævi. The age at which they were first seen varied from 7 weeks to 5 years, averaging 7 months. They were reexamined at intervals of 6 months or less for up to 23 months on average. About half attended regularly until the age of 5 years. Most of the others were examined at the age of 5 years or over, but in a few cases the information came from the parents by letter. Apart from the age of onset and the rate of growth, all changes recorded are those actually observed at the time of examination or the final letter, but they may have arisen earlier in the intervals between examinations.

Incidence

I can make no firm estimate of the incidence because I rely solely on referred cases. But these 140 children, and 32 others not included in the series because they could not be followed up, were referred to me as the only dermatologist working in an area where the population is relatively stable. The majority of these patients were born in the years 1948–51 inclusive. By comparing them with the number of children born in this area and surviving 1 year, the annual incidence seems to be not less than 0·3%, 0·6%, 0·5%, and 0·35%, with an average of 0·45%.

TABLE II—SITE OF 170 HÆMANGIOMATA

Site	No. of cases
Face	34 (20%)
Back	24 (14%)
Scalp	23 (14%)
Chest	19 (11%)
Abdomen	14 (8%)
Arm	10 (6%)
Buttock	9 (5%)
Thigh	8 (5%)
Leg	7 (4%)
Neck	7 (4%)
Forearm	6 (3·5%)
Genitalia	5 (3%)
Hand	2 (1%)
Hip	1 (0·75%)
Flank	1 (0·75%)

Of these 140 children 108 had one lesion only. 53 were boys and 87 were girls. Pregnancy had been normal in all but 6 cases in which the complications were toxæmia (2), measles at 2 months, myomectomy at 3 months, an antepartum hæmorrhage, and an accident at 7 months causing fracture of the clavicle. Labour was normal in all but 9 cases, where there was prematurity (4), blue asphyxia, retained placenta, breech presentation (2), and forceps delivery. In no case was any other congenital abnormality found. Of 93 siblings alive when the children were first seen, 22 had then, or had had, a similar lesion. 4 of the patients were twins, identical in 2 cases, but none of the opposite twins had a hæmangioma.

Age of Onset

The ages at which the mothers had first observed a lesion are shown in table I.

Site of Lesion

The sites of the 170 lesions are shown in table II.

Treatment

Of these 170 nævi 14 were treated with carbon-dioxide snow, 15 by irradiation, and 1 by diathermy. The other 140 were untreated.

The Untreated Cases

Cavernous hæmangiomata grow at varying rates for 6 to 12 months before regression, the first sign of which is a pale greyish-blue stippling in the previously bright red surface. Further paling and flattening proceed in the next few years. In some cases, by the age of 5 years, the

TABLE III—AVERAGE AGES FOR CHANGES IN 140 UNTREATED HÆMANGIOMATA (EXTREME LIMITS ARE SHOWN IN PARENTHESES)

Changes	Dermal	Mixed	Hypodermal
Growth ceased	8½ mos. (2–36)	12 mos. (3–48)	21 mos. (9–36)
Paling began	15 ,, (3–48)	9 ,, (2–36)	..
Flattening began	16½ ,, (4–48)	18 ,, (4–36)	23 ,, (14–36)
Paling completed	5½ yr. (1¼–8)	5 yr. (2¼–8)	..
Flattening completed	5½ ,, (¾–8)	4¾ ,, (1¼–8)	3½ yr. (2¼–6)

TABLE IV—PROPORTION OF HÆMANGIOMATA SHOWING RESIDUAL CHANGES AFTER 5 YEARS

Residual changes	Dermal (90)	Mixed (47)	Hypodermal (3)	Total (140)
Telangiectasia:				
Nil	55 (61%)	25 (53%)	3 (100%)	83 (59%)
Slight	29 (32%)	19 (41%)	..	48 (34%)
Severe	6 (7%)	3 (6%)	..	9 (7%)
Pallor:				
Nil	73 (80%)	33 (70%)	3 (100%)	109 (77%)
Slight	13 (15·5%)	6 (13%)	..	19 (14%)
Severe	4 (4·5%)	8 (17%)	..	12 (9%)
Puckering:				
Nil	74 (82%)	30 (64%)	2 (67%)	106 (77%)
Slight	13 (14·5%)	12 (25%)	1 (33%)	26 (17%)
Severe	3 (3·5%)	5 (11%)	..	8 (6%)
No trace	51 (57%)	24 (51%)	2 (67%)	77 (55%)

lesion cannot be detected. In others there remain slight central pallor, a faint pink rim, and a few telangiectases running across the centre. In a few the skin is left slightly puckered, with loss of elasticity. Many such lesions in this series were observed for longer than 5 years, and this puckering gradually became less noticeable. The pallor, as one would expect, was greatest in lesions which had ulcerated.

Of the 140 untreated nævi 90 were dermal, 3 were hypodermal, and 47 were mixed. Table III shows the average age at which changes occurred.

Table IV shows the proportion in each group with residual changes.

The relation between the maximum dimension of the lesion and the findings at 5 years is shown in table V.

TABLE V—RELATION BETWEEN MAXIMUM DIMENSIONS OF THE LESIONS AND THE FINDINGS AT 5 YEARS

Maximum dimension	<1 cm.	1–2 cm.	2–3 cm.	>3 cm.
Total	20	55	40	25
No trace at 5 yr.	10 (50%)	37 (67%)	19 (48%)	11 (44%)

Table VI shows no significant relation between the final result and the age at which the lesion appeared.

The general impression that rapid growth of a lesion in the early stages indicates a better prognosis was not confirmed, as is shown in table VII.

The final result was not related to the site of the nævus, though it was usually better than average on the abdomen and worse on the back. This cannot be due to any special tendency to ulceration on the back, as is shown by table VIII, which gives the site and type of the 16 nævi which ulcerated.

The risk of ulceration has been used as an argument in favour of treatment. In my experience with these 16 ulcerated nævi, in which no special precautions were taken, hæmorrhage never gave rise to serious parental anxiety; nor was the child's general condition impaired. Coagulation and necrosis gradually proceeded, and a yellow slough formed at the base of the ulcer. This disintegration often remained localised to part of the hæmangioma, and never extended beyond its deep or lateral borders to involve healthy tissue.

No bacterial studies were made, but any secondary infection did not lead to erythema, œdema, induration of the surrounding skin, lymphadenitis, or fever. No antiseptics or antibiotics were used, the ulcers being dressed with paraffin gauze or zinc and castor-oil ointment. The ulcers healed spontaneously in 1–6 months, leaving a white atrophic scar. They were associated with earlier resolution of the nævus than would otherwise have been expected.

Ulceration was rather commoner in the larger nævi, and 2 cases are worth special mention.

The lesions were both of the mixed variety. One involved the whole posterolateral quadrant of the head and neck, including the pinna; the other extended from just below the elbow to the back of the hand, almost encircling the limb. The usual treatment was adopted with the same result. Both children were miserable but otherwise remained well. The upper limb retained full function; in the scalp at least 50% of normal hair growth was preserved, although the pinna will need plastic reconstruction eventually.

TABLE VI—RELATION BETWEEN AGE AT WHICH LESIONS APPEARED AND THE FINAL RESULTS

Age of onset	No. of nævi	No trace
Birth	35	19 (56%)
1st wk.	21	10 (48%)
2nd ,,	37	21 (57%)
3rd ,,	10	5 (50%)
4th ,,	18	12 (67%)
2nd mo.	9	3 (33%)
3rd ,,	4	4 (100%)
4th ,,	4	2 (50%)
6th ,,	2	1 (50%)
Total	140	77

TABLE VII—RELATION BETWEEN RATE OF GROWTH AND PROGNOSIS

Rate of growth	Rapid	Slow
Total no.	42	98
Resolution complete at 5 yr.	21 (50%)	56 (57%)
Resolution incomplete ,, ,,	21 (50%)	42 (43%)

Only a little more than half of these nævi became involuted completely without trace by the age of 5 years, but in only 1 case did the mother express or show dissatisfaction with the result at that stage. Many nævi which had not entirely disappeared have been observed for much longer, and they have continued to improve although more slowly.

Results of Treatment

The total number of nævi treated is too small for any serious comparison. In the 15 cases treated by irradiation the total dose varied between 700r and 3200r. No radiodermatitis was seen, and, on the whole, the lesions resolved at much the same rate and to the same extent as in the untreated cases. Carbon-dioxide snow was used very cautiously (never for more than 10 seconds at each treatment), with the same final results. In the 1 case treated by diathermy by a surgeon, the result at 5 years was deplorable.

TABLE VIII—SITE AND TYPE OF THE 16 NÆVI WHICH ULCERATED

Site	Dermal	Mixed	Total
Back	3	..	3
Scalp	2	2	4
Genitalia	..	1	1
Thigh	..	2	2
Hip	1	..	1
Buttock	1	1	2
Face	..	2	2
Forearm	..	1	1
Total	7	9	16

Discussion

The highly satisfactory findings in the untreated cases were much the same as in other reported series and must be taken as a basis for comparison with the results of all methods of treatment.

Excision

Several heroic operations involving extensive excision and grafting are reported in infants. Apart from the

grave risks of anæsthesia, hæmorrhage, and shock, and the expenditure of skill and time, the final cosmetic results are unpredictable (as with all grafts) and the donor areas may be unstable in later life. On the other hand, if operation is deferred and performed only when natural resolution will clearly be unsatisfactory, simple excision of superfluous puckered skin may suffice, and, at the worst, a more elaborate procedure can be undertaken with far less danger.

Injection of Sclerosing Fluids

The results are uncertain, if not dangerous, and a general anæsthetic is necessary.

Refrigeration

This is only suitable for dermal lesions, and, unless performed with great care, may cause severe atrophy. It is perhaps indicated if the infant is seen very soon after the hæmangioma appears, particularly if the lesion is small but growing rapidly, and if the parents are willing to accept the risk of a small scar.

Irradiation

In some areas it is difficult, if not impossible, to irradiate the lesion without damaging structures such as the gonads, female breast tissue, growing epiphyses of bones, or hair roots. Untreated cavernous hæmangiomata of the scalp, unless ulcerated, resolve with little or no permanent loss of hair.

Walter (1953) compared 83 untreated lesions with 88 treated by irradiation with a dose of 400r. The results were similar, being satisfactory in 96%. With a dose of 800r regression was slightly quicker, but the final result was the same. He concluded that the radiosensitivity of the lesions was not lowered materially by waiting until the age of 1 year, and not lowered seriously until 5 years.

Brain and Calnan (1952) recommended a total dose of 1200–1500r in divided doses, but said that " much of the credit for the ultimate good result belongs to nature ".

Larger doses may give much quicker resolution at the cost of permanent radiodermatitis, which is seen occasionally in older patients who were treated when radiotherapy was used with more enthusiasm and less discretion.

van der Werf (1954) compared the results in school children and gave these figures:

Treatment	Total no.	Satisfactory	Moderately satisfactory	Unsightly
Nil	59	46 (*78%*)	12 (*20%*)	1 (*2%*)
Cauterisation	68	24 (*35%*)	34 (*50%*)	10 (*15%*)
Radiation ..	62	15 (*24%*)	25 (*40%*)	22 (*36%*)
Surgery ..	136	30 (*22%*)	56 (*41%*)	50 (*37%*)

Thus cavernous hæmangiomata almost invariably undergo spontaneous resolution, more than half of them disappearing completely by the age of 5 years. When some traces remain at that age further cosmetic improvement may reasonably be expected. Any residual telangiectasia can be treated easily by electrolysis, galvanocautery, or unipolar diathermy needle during adolescence, when unsightly puckering or atrophy presents a comparatively simple problem to the plastic surgeon.

The only real indication for treatment is when a cavernous hæmangioma interferes seriously with functions such as vision, breathing, or sucking. Even then any treatment, apart from simple excision and primary suture, which hastens natural resolution is likely to produce a less satisfactory cosmetic result than if no treatment were given. This consideration is of special importance on exposed areas, and the arguments in favour of letting nature take its course apply with more, not less, force when the lesion is so situated.

Summary

The changes in 140 untreated cavernous hæmangiomata are compared as far as possible with the results in treated cases. Because these lesions almost always resolve spontaneously, more than half disappearing by the age of 5 years, no treatment is recommended.

REFERENCES

Brain, R. T., Calnan, C. (1952) *Brit. J. Derm.* **64**, 147.
Duncan, J. (1885) *Edinb. med. J.* **1**, 401.
Lister, W. A. (1938) *Lancet*, i, 1429.
Rhonchese, F. (1953) *Amer. J. Surg.* **86**, 376.
van der Werf, E. (1954) *Ned. Tijdschr. Geneesk.* **98**, 676.
Wallace, H. J. (1953) *Brit. J. plast. Surg.* **6**, 78.
Walter, J. (1953) *J. Fac. Radiol., Lond.* **5**, 134.

REIMPLANTATION OF LOBES OF THE LUNG
AN EXPERIMENTAL TECHNIQUE

C. E. HUGGINS *
M.D. Harvard

From the Division of Experimental Biology, National Institute for Medical Research, Mill Hill, London, N.W.7

FOR centuries surgeons have had visions of transplanting organs from one individual to another. Direct scientific investigation of this problem was started by Carrel who described a satisfactory technique for blood-vessel suture in 1902, and reported successful autotransplantation of a canine kidney in 1906 (Carrel and Guthrie 1906). The feasibility of renal transplantation has now been demonstrated experimentally in animals and in selected clinical cases (Dempster 1950, Murray et al. 1958).

Juvenelle et al. (1951) reported 1 survivor from an unstated number of dogs subjected to pneumonectomy and replantation of the vessels and bronchus of the right lung. Davis et al. (1952) had 5 animals which survived for from 20 minutes to 8 days following lung homotransplantation with suture of the individual hilar structures of the left lung. Neptune et al. (1953) and Hardin and Kittle (1954) have reported series of canine lung transplants. However, both of these latter groups anastomosed patches of atrium containing both pulmonary veins rather than the veins draining the individual lobes. Borrie and Montgomerie (1958a) reported excision and reimplantation of the lung in sheep, but had no survivors for longer than six days.

Moore et al. (1959) have recently reported an experimental method for homotransplantation of the liver of dogs. To protect the organ against anoxia and the recipient against the effects of blood-pooling, they use the techniques of differential intraperitoneal hypothermia and venous shunts which were developed for partial hepatectomy by Huggins et al. in 1957.

The development of suitable banking methods is necessary, both for experimental work and for clinical use when the problem of homograft reaction is solved.

The protective action of glycerin against the lethal effect of freezing and thawing fowl spermatozoa was first demonstrated by Polge et al. in 1949. Since this report the glycerin-freezing technique has been used to preserve a wide variety of cells and pieces of tissue, including endocrine tissue (Parkes 1958), red blood-cells (Jones et al. 1957), bone-marrow (Barnes and Loutit 1955, Ferrebee et al. 1959), and cornea.

We perfused dog kidneys with solutions containing glycerin in attempts to extend the applicability of the glycerin-freezing technique to preservation of whole organs. These experiments were unsuccessful owing to

* This work was done while the author was Moseley travelling fellow from Harvard Medical School, Boston, U.S.A. Present address: Massachusetts General Hospital, Boston, U.S.A.

the development of massive renal œdema and necrosis following transplantation. The difficulties of perfusing kidneys have been known for years (Whittaker and Winton 1933).

The possibility of using the left lower lobe of the dog lung as the test organ was then studied. The chief advantages of pulmonary tissue for this purpose are ease of perfusion and the ability to mould it gently into any desired shape for freezing and thawing. A single lobe was selected to give a relatively uniform mass for heat transfer. The remaining lobes on the same side were removed so that all treated tissue would be on the left with the intact right lung serving as the control.

Method

Dogs of various breeds and each sex were used in these experiments. They were selected for large size and ranged in weight from 55 to 91 lb. All operations were done with full aseptic precautions using intravenous pentobarbitone sodium (30 mg. per kg.) for anæsthesia. Artificial ventilation with oxygen was maintained through a cuffed endotracheal tube by means of a Starling respiration pump. Expiratory resistance of 10 ml. of water was applied while the thorax was open.

The incision was made through the bed of the left sixth rib. This gave maximum exposure for carrying out the pulmonary venous anastomosis. The two divisions of the upper lobe were removed, the upper-lobe bronchus being divided close to the main bronchus. Exposure in subsequent steps was facilitated by dividing the superior pulmonary vein intrapericardially.

The pulmonary artery was freed from its bifurcation to its entrance into the lower lobe. The pericardium anterior to the inferior pulmonary vein was incised and the vein freed posteriorly to the junction with its opposite member from the right. The peribronchial structures were divided, but ligated only on the cardiac side. When the lobe was attached only by its bronchial and pulmonary vascular connections, these structures were clamped and divided, and the lobe was removed. The bronchus was transected within 1 cm. of its entrance into the lobe, the pulmonary vein in its midportion, and the pulmonary artery at any convenient point. No anticoagulants were used when the lobe was out of the body.

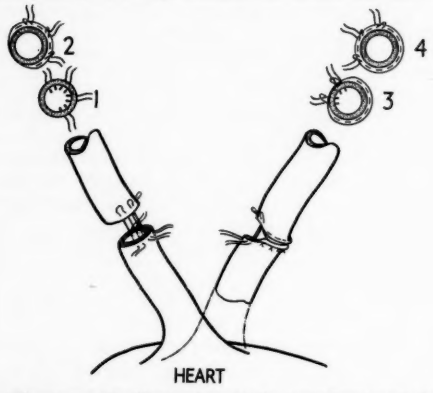


Fig. 1—Diagrammatic illustration of the technique used for the pulmonary venous anastomosis.

To reimplant the lobe 5–0 arterial-silk everting mattress sutures were laid in the cut edges of the inferior pulmonary vein at 3, 5, 7, and 9 o'clock (fig. 1). These were tied and additional mattress sutures placed at 4, 6, and 8 o'clock. The lobe was then shifted posteriorly to expose the anterior wall of the anastomosis, which was completed by laying mattress sutures at 11 and 1 o'clock, tying them, and ending with sutures at 10, 12, and 2 o'clock.

The bronchus was anastomosed with interrupted stitches of 4–0 silk. At this point the lobe was re-expanded and any air leakage from the suture line corrected.

The pulmonary artery was anastomosed with doubly interrupted continuous over-and-over sutures of 5–0 arterial silk. The clamps were removed from the pulmonary vessels and additional sutures placed as necessary to achieve hæmostasis.

A loosely tied mattress suture of 0 chromic catgut was found to be an effective way of tacking the anterior edge of the lobe to the pericardium to prevent postoperative volvulus.

The chest was closed with interrupted linen sutures in the rib bed and running sutures to the muscles and skin. An intercostal catheter was connected to −10 cm. of water suction for the first 30 minutes following cessation of artificial ventilation, and to water-seal drainage for the next 2 hours. At the end of this time the catheter was removed and the dog returned to its cage.

Postoperatively the dogs received their regular diet and care. In addition they were given 750 mg. of oxytetracycline orally for each of the first 5 postoperative days.

With the exception of 1 animal killed 12 days after operation, the animals which survived were killed at intervals from 1 to 4 months. At the end of the experiment the animals were anæsthetised and differential oxygen consumption measurements were made and radiographs taken. Photographs and anatomic studies were done at necropsy.

Results

This type of operation was performed on 16 dogs. The only survivor from the first 9 was the 1st animal. The causes of death of the other 8 were as follows.

Cause	*No.*
Thrombosis of the inferior pulmonary vein	4
Gangrene of the bronchus with pneumothorax	3
Volvulus of the transplant	1

Hæmoptysis occurred before death in the 4 animals dying from inferior pulmonary vein thrombosis; they died 1, 1, 2, and 4 days postoperatively. At postmortem examination prominent features were 200–500 ml. of bloodstained pleural effusion, and an enormously enlarged congested lobe. Microscopic sections showed degenerate necrotic lung.

Close scrutiny of the pulmonary venous anastomoses showed the thrombus to have originated on a minute area of cut pulmonary venous wall in contact with the bloodstream. These early anastomoses were done with a doubly interrupted continuous suture. Since adopting the interrupted everting mattress suture technique, which prevents infolding even the minutest amount of vessel wall, we have had no further difficulty with this problem.

The 3 dogs which died from gangrene of the bronchus did so on the 2nd, 5th, and 6th days postoperatively. None of these animals had auscultatory evidence of pneumothorax on the day after operation. Air leakage developed late and was progressive despite aspiration. Gross and microscopic examination of the lobar bronchus showed ischæmic changes which were most severe near the anastomosis. The bronchus in these dogs had been transected at a convenient point 1·5–2·0 cm. from its entrance into the lobe. Since dividing the bronchus within 1 cm. of the lobe we have had no further difficulty with bronchial necrosis.

Interrupted sutures tacking the lobe to the pericardium had cut through the thin pleura in the dog which died from volvulus. A heavy catgut mattress restraining suture which tightens only if the lobe starts to shift position has eliminated this complication.

The next 7 dogs have successively survived the operation. One dog had a pneumothorax which persisted for 6 days following operation. A stricture developed at the bronchial anastomosis and the lung did not function. The vascular anastomoses were intact at necropsy 2 months postoperatively.

The dogs were tested for function of the transplanted lobe by occluding the right main bronchus for 40 minutes with a clamped cuffed endotracheal tube. With the exception of the 1 animal with bronchostenosis, all animals survived this procedure and showed no abnormal neurological signs when they had recovered from anæsthesia. The oxygen consumption from the right and left sides was also measured to give a more accurate indication of pulmonary function. Typical results are shown in fig. 2. A radiograph is shown in fig. 3.

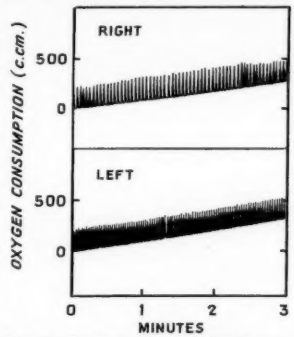


Fig. 2—Oxygen consumption (c.cm. per min.) measured alternatively from the right and left sides.

At necropsy there were postoperative adhesions between the lobe, heart, and chest wall. The transplanted lobe appeared normal on macroscopic and microscopic examination.

Discussion

Intact lung has both pulmonary and bronchial vascular systems. Transplanted lung, on the other hand, does not have the advantage of dual blood-supply. Indeed, removal and replacement of a pulmonary unit is the only certain experimental method for dividing all of its bronchial blood-supply. The consequences of absent bronchial blood-supply are twofold. First, interruption of pulmonary blood-flow completely devitalises the tissue and leads to actual necrosis whether the point of circulatory occlusion be arterial, capillary, or venous. Secondly, all bronchus outside the confines of the lobes must be nourished by collateral circulation from the pulmonary to bronchial systems.

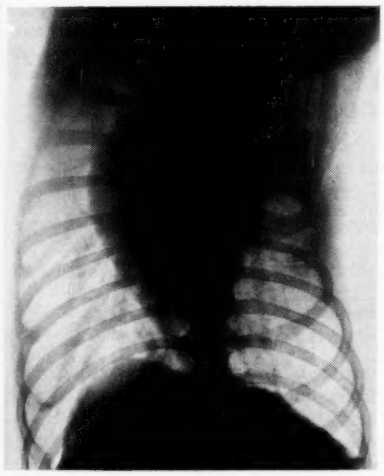


Fig. 3—Right posterior oblique (A.P.) radiograph of chest 21 days after left upper and lower lobectomy with lower-lobe reimplantation.

Congestive necrosis of the transplanted lobe was seen in the 4 animals whose pulmonary venous anastomoses clotted. In each case the thrombus arose on infolded pulmonary venous wall. This observation prompted a study of the relative thromboplastic activity of blood-vessels throughout the body (Huggins 1959). The activity of pulmonary veins was found to be equivalent quantitatively and qualitatively to heart, femoral arteries, and femoral veins. These structures have an action many times that of thoracic or abdominal aorta, thoracic vena cava, or pulmonary artery. Medium-size arteries and veins, pulmonary veins, and heart are the only blood-vessels of the body that contain large amounts of muscle in their walls. The similarity of their thromboplastic activity is presumably due to this element. It appears that the thromboplastic activity of the blood-vessel walls may be a more important factor predisposing to early thrombosis of vascular anastomoses than mechanical turbulence or stasis of blood-flow. A suture technique that assures complete eversion of the cut edge of the pulmonary vein has eliminated the complication of thrombosis.

We did not see bronchial necrosis when the main bronchus was divided within 1 cm. of the most proximal segmental orifice of the lower lobe. This landmark generally corresponds to the proximal edge of the lobe externally, but varies somewhat with the breed of dog. Collateral circulation from the pulmonary circuit was not sufficient to nourish the bronchus if it was transected farther than 1·5–2·0 cm. from the segmental orifice.

The bronchus and lung tissue within the confines of the lobe were normal functionally and anatomically as far as they were tested. The lung substance, under ordinary conditions of life, appears to tolerate interruption of bronchial blood-supply without apparent effect.

Mathes et al. (1932) attempted interruption of the bronchial arteries to one of the lower lobes of a dog lung by stripping all the areolar tissue from around the pulmonary vessels and bronchus. "At autopsy the lobe was normal and injection showed branches of the bronchial artery remaining in the submucosa of the bronchus."

The multiplicity of pathways for bronchial blood to reach the lung led Ellis et al. (1951) to conclude that few workers who have tried to interrupt bronchial flow have actually accomplished this end. They attempted to overcome this problem by injecting vinyl acetate plastic into the right posterior bronchial artery of dogs, and found necrosis of the right stem bronchus and lobar bronchi. It must be remembered, however, that their technique not only interrupts bronchial blood-flow, but prevents the entrance of collateral circulation from the pulmonary system as well.

The extensive network of vessels within the bronchial wall may be seen on histological examination of a normal bronchus. Their presence is occasionally demonstrated by persistent bleeding from the bronchial stump during pulmonary resection. Division and suture of the bronchus is the only certain method of interrupting these vessels and should be an integral part of experiments designed to demonstrate effects of absent bronchial flow.

Bogardus (1958) studied the effect of temporary occlusion of a main pulmonary artery plus temporary or permanent ligation of the bronchial arteries, as tested by survival following contralateral pneumonectomy. He found a decrease in the survival-rate of dogs with divided bronchial vessels whether the opposite lung was removed at the same time or later. The conclusion was drawn that bronchial-artery division played an important role in the death of these dogs, but the mechanism of this action was not clear. He also observed that the lungs of these animals did not aerate with artificial ventilation as well as those of intact lungs.

We have made similar observations in dogs with pulmonary œdema and have interpreted Bogardus' results as due to impaired lymphatic drainage rather than to interruption of bronchial blood-flow per se. This formed the basis for our decision to ligate hilar structures only on the cardiac side. We considered the possibility of a pleural effusion from open lymphatics less dangerous than

obstruction to lymphatic outflow from the transplant. Back-bleeding from transected bronchial vessels was never noted.

It would appear that the differences in the reported effects of bronchial circulatory interruption may be explained by a number of considerations: (1) differences in the point of occlusion of the bronchial vessels, (2) failure to divide and suture the bronchus to the portion of lung under examination, (3) obstruction to collateral circulation from the pulmonary system by an intravascular mass, (4) concomitant impairment of lymphatic drainage.

The technique of excision and reimplantation of portions of the lung assures division of all bronchial blood-supply, without interference with collateral blood-flow and with minimal impairment of lymphatic drainage.

In our series, the survival-time for dogs with unsuccessful autotransplants ranged from 1 to 6 days, with an average of 3·3 days. Although they had no longterm survivors, Borrie and Montgomerie (1958a) had sheep which lived 6 days following operation. They tested pulmonary function in these animals by differential bronchospirometry (Borrie and Montgomerie 1958b). Neptune et al. (1953) reported an average survival of 9 days for variously treated lung homografts, and 1 year for their one autograft control. Hardin and Kittle (1954) reported survival of untreated lung homografts for 1 to 12 days, and 1 to 4 days for "second set" grafts (Hardin 1956). The relatively long survival of occasional animals with unsuccessful lung autotransplants makes proper statistical comparison essential in lung-homotransplantation experiments.

At present surgeons are attempting to extend the limits of operability for poor-risk patients with carcinoma of the lung by resection of the upper lobe and a sleeve of main bronchus with anastomosis of the lower lobe proximally. Price Thomas (1959) and Jones (1959) have reported large series of such cases. If the longterm results of their studies prove sufficiently encouraging, much wider excision of the main bronchus and hilar structures with reimplantation of the lower lobe at a higher level might be undertaken. The principles learned from these experiments would be applicable.

Summary

Excision and reimplantation of the left lower lobe of the dog lung has been accomplished by suture of the divided pulmonary vessels and bronchus.

Excision abolishes the bronchial blood-supply to reimplanted lobes of the lung. The pulmonary venous anastomoses from these lobes were found to have a greater tendency to early thrombosis than would be expected from anastomoses of comparable-sized systemic arteries or veins. When early thrombosis recurred the lobes were completely devitalised and underwent necrosis. A satisfactory method for preventing early thrombosis was found.

Collateral circulation from the pulmonary to bronchial vascular systems was adequate to nourish the bronchus if the stump projected less than 1·0 c.m from the lobe. If the stump was 1·5–2·0 cm. long, it became gangrenous and the animal died from pneumothorax.

With the exception of 1 animal, in which stenosis of the bronchial anastomosis developed, surviving animals had normal lobes, functionally and anatomically, as far as tests indicated.

This technique could be used in experiments on transplantation and preservation of organs, and to study the effect of bronchial-artery division. The principles of the technique would apply to reimplantation of lung tissue clinically.

I would like to thank Sir Charles Harington, F.R.S., and Dr. A. S. Parkes, F.R.S., for permission to work in the Division of Experimental Biology. I would also like to thank them and Dr. Audrey U. Smith for their many helpful suggestions during this work. This work could not have been done without the valuable technical assistance of Mr. F. Crisp and Miss N. O. Reid. Pfizer Ltd., Folkestone, Kent, kindly donated the oxytetracycline ('Terramycin') used in these experiments.

REFERENCES

Barnes, D. W. H., Loutit, J. F. (1955) *J. nat. Cancer Inst., Wash.* **15**, 901.
Bogardus, G. M. (1958) *Surgery*, **43**, 849.
Borrie, J., Montgomerie (1958a) *Proc. Univ. Otago med. Sch.* **36**, 9.
— — (1958b) *ibid.* **36**, 10.
Carrel, A. (1902) *Lyon méd.* **98**, 859.
— Guthrie, C. C. (1906) *J. Amer. med. Ass.* **47**, 1648.
Davis, H. A., O'Connor, J. P., Coloviras, G. J., Strawn, D. L. (1952) *Arch. Surg.* **64**, 745.
Dempster, W. J. (1950) *Ann. R. Coll. Surg. Engl.* **7**, 275.
Ellis, F. H., Grindlay, J. H., Edwards, J. E. (1951) *Surgery*, **30**, 810.
Ferrebee, J. W., Atkins, L., Lochte, H. L., Jr., McFarland, R. B., Jones, A. R., Dammin, G. J., Thomas, E. D. (1959) *Blood*, **14**, 140-147.
Hardin, C. A. (1956) *Surg. Forum Amer. Coll. Surg.* 1955, p. 565.
— Kittle, C. F. (1954) *Science*, **119**, 97.
Huggins, C. E. (1959) Unpublished.
— Carter, E. L., McDermott, W. V., Jr. (1957) *A.M.A. Arch. Surg.* **74**, 327.
Jones, N. C. H., Mollison, P. L., Robinson, M. A. (1957) *Proc. roy. Soc. B.* **147**, 476.
Jones, P. H. (1959) *Ann. R. Coll. Surg. Engl.* (in the press).
Juvenelle, A. A., Cittet, C., Wiles, C. E., Stewart, J. D. (1951) *J. Thorac. Surg.* **21**, 111.
Mathes, M. E., Holman, E., Reichert, F. L. (1932) *ibid.* **1**, 339.
Moore, F. D., Smith, L. L., Burnap, T. K., Dallenbach, F. D., Dammin, G. J., Gruber, V. F., Shoemaker, W. C., Steenburg, R. W., Ball, M. R., Belko, J. S. (1959) *Transplant. Bull.* **6**, 103.
Murray, J. E., Merrill, J. P., Harrison, J. H. (1958) *Ann. Surg.* **148**, 343.
Neptune, W. B., Redondo, H., Bailey, C. P. (1953) *Surg. Forum Amer. Coll. Surg.* 1952, p. 379.
Parkes, A. S. (1958) *J. Endocrin.* **17**, 337.
Polge, C., Smith, A. U., Parkes, A. S. (1949) *Nature, Lond.* **164**, 666.
Rycroft, B. W. (1955) Corneal Grafts; p. 199. London.
Thomas, C. Price (1959) *Ann. R. Coll. Surg. Engl.* **24**, 345.
Whittaker, S. R. F., Winton, F. R. (1953) *J. Physiol.* **78**, 339-369.

ACUTE HÆMOLYTIC ANÆMIA AND METHÆMOGLOBINURIA PRODUCED BY PHENACETIN

I. B. HOUSTON
M.B. Manc., M.R.C.P.

SENIOR HOUSE-OFFICER, UNIVERSITY DEPARTMENT OF MEDICINE

A. M. BARLOW
M.B. Manc.

REGISTRAR, UNIVERSITY DEPARTMENT OF HÆMATOLOGY
MANCHESTER ROYAL INFIRMARY

HÆMOLYTIC anæmia and intracellular methæmoglobinæmia due to chemical agents are not uncommon; Wintrobe (1956) recorded them after exposure to aniline derivatives, nitro compounds, and sulphonamides. When phenacetin is the causal agent, most patients have had moderate or large doses of the drug for a long time; such cases of chronic hæmolysis are well documented (Jasinski and Müller 1950, Marti 1958). Acute hæmolysis due to small doses of phenacetin is much rarer, and phenacetin is not generally acknowledged as a cause of acute hæmolytic anæmia.

Dern et al. (1955) studied the hæmolytic action of primaquine and showed that 10% of American Negroes have an inherent defect in their red blood-cells (R.B.C.s) making them susceptible to hæmolysis by primaquine and 8-aminoquinoline compounds used for treating malaria. This defect is less common in Europeans, but its exact incidence is uncertain. R.B.C.-survival studies, using radioactive chromium, show that such cells are also abnormally liable to hæmolysis in the presence of phenacetin, acetanilide, and sulphanilamide. We believe this defect is present in the R.B.C.s of the patient we describe, in whom a small dose of phenacetin caused gross hæmolysis and methæmoglobinuria. The case illustrates the

greater variety of diseases encountered since the immigration of more non-Europeans during the past few years. Related instances of drug induced hæmolysis may, in future, be commoner in this country.

Case-report

A 28-year-old coloured man, a student from Ghana, was seen on May 28, 1958. For 2 weeks he had had headaches, malaise, generalised muscular aches, and shivering. He had had malaria in Ghana, with no recurrence since he came to England 5 years previously. There was no family history of anæmia or jaundice. His temperature was 101·4°F, and the conjunctivæ were injected, but no other abnormality was detected, and chest radiographs were normal. He was thought to have an influenza-like illness, and was advised to rest in bed and take compound aspirin tablets (*B.P.C.*), 1 q.i.d., for symptomatic relief.

4 days later he was seen again; his former symptoms were unchanged, but 24 hours after first attending hospital his urine had become dark reddish-brown. Because this persisted, he was admitted to hospital on June 2. He had then taken 21 compound aspirin tablets containing a total of 3·5 g. of phenacetin. In the past he had occasionally taken an isolated analgesic tablet containing phenacetin. His conjunctivæ were still injected, his temperature was 101·2°F, and his urine was still dark. He was given only ascorbic acid, sodium-citrate mixture (*B.P.C.*), and later iron by mouth. He was anorexic and lethargic, and his pyrexia (99·8–101·2°F) continued unremittingly for 7 days. He continued to pass dark reddish-brown urine for 5 days; on the 6th day it was less discoloured, and on the 8th day it was normal. Simultaneously his general condition improved, his appetite returned, and he became apyrexial. The urinary output varied between 1·4 and 1·7 litres daily during the first 10 days. He was discharged from hospital on July 3, and has remained well.

Routine Investigations

On June 2 the hæmoglobin was 13·9 g. per 100 ml.; 10 days later it fell to 8·3 g., and then it rose steadily to 13·3 g. $2^1/_2$ months later. These changes in hæmoglobin level, together with changes in the percentage of erythrocytes containing Heinz bodies and of reticulocytes are shown in fig. 1. On June 2 the white-blood-cell count was 7400 per c.mm., with a normal differential count, and the platelet-count was 240,000 per c.mm.

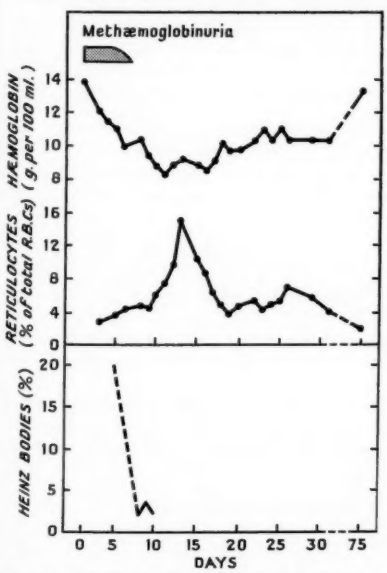


Fig. 1—Changes in hæmoglobin, reticulocytes, and R.B.C.s containing Heinz bodies, related to methæmoglobinuria.

No spherocytes, ovalocytes, or target-cells were seen in peripheral blood-films.

The urine contained no R.B.C.s, and no other abnormal constituent was found chemically or microscopically; cultures were sterile. The blood-urea was 28 mg. per 100 ml., serum-albumin 3·5 g. per 100 ml., and serum-globulin 2·8 g. per 100 ml.

Several blood-smears, both thick and thin, were examined for malaria parasites, but none were found. Neither sickling nor abnormal hæmoglobins could be demonstrated. The Donath-Landsteiner test, Ham's test, direct and indirect Coombs' tests, the Wassermann reaction, Kahn test, and the Paul-Bunnell test were all negative. Schumm's test for methæmalbumin was negative on June 4, but it had become positive 4 days later. The R.B.C. osmotic fragility was normal, and the antibody-titres to *Brucella abortus*, *Br. mellitensis*, *Streptococcus MG*, and various salmonellæ were all within normal limits. Radiographs of the chest showed no abnormality; culture of the sputum and of a throat-swab yielded normal upper-respiratory-tract flora only. Blood-cultures taken on June 4, 7, and 8 were sterile after 10 days ærobic and anærobic incubation.

Spectroscopic Investigations

The patient's urine and plasma, and the hæmolysate from his washed R.B.C.s, were examined with a direct-vision spectroscope. The urine and plasma apparently contained a mixture of methæmoglobin and oxyhæmoglobin, but, in view of the work of Fairley (1941), the plasma-pigments were most probably a mixture of methæmalbumin and oxyhæmoglobin. The hæmolysate from the washed R.B.C.s, however, showed only the absorption bands of oxyhæmoglobin. The absorption spectrum of the urinary pigments was plotted with a 'Unicam S.P.' 500 spectrophotometer, and absorption maxima at 630, 577, 536, and 490 mμ were obtained, confirming the presence of methæmoglobin in the urine. As the absorption bands of methæmoglobin and metmyoglobin are rather close, this examination did not entirely exclude the possibility that the pigment in the urine and plasma was metmyoglobin. The two pigments can be more clearly distinguished by comparing their carboxy derivatives (Spaet et al. 1954), the absorption maxima of the α-bands being at 570 mμ. for carboxyhæmoglobin, and at 579 mμ. for carboxymyoglobin. Accordingly the absorption spectra of the carboxy derivatives of the urinary and plasma pigments were compared with that of a solution of carboxy-hæmoglobin over the wavelength range 560–580 mμ. The peak of the absorption curve for all these pigments was at 569 mμ., confirming that the urinary and plasma pigments were derived from hæmoglobin and not from myoglobin.

TESTS FOR IN-VITRO HEINZ-BODY PRODUCTION

Type of cells	R.B.C.s (%) containing five or more Heinz bodies after exposure		
	to acetylphenyl-hydrazine	to phenacetin	to buffer only
Normal	2·5	0	0
Patient's ..	81·0	0	0

In-vitro Erythrocyte-sensitivity Tests

Heinz-body formation.—Beutler et al. (1955a), when investigating the hæmolytic effect of primaquine, described an in-vitro test to distinguish those whose R.B.C.s were sensitive to the hæmolytic action of this drug. Briefly, the test involves incubation of the patient's red blood-cells in a buffered solution of acetylphenylhydrazine, after which they are stained with a crystal-violet solution to demonstrate the Heinz bodies; the percentage of R.B.C.s containing five or more Heinz bodies is then calculated. We did this test, using both the patient's R.B.C.s and those of a normal donor; in addition we incubated the R.B.C.s of both in a 100 mg. per 100 ml. buffered solution of phenacetin, and examined them for Heinz bodies.

Beutler et al. (1955a) showed that, if more than 32·5% of R.B.C.s contained five or more Heinz bodies after incubation with acetylphenylhydrazine solution, the patient should be classed as "sensitive". The results (see table) show conclusively that our patient fell into this group. Our interpretation is not altered by failure of the phenacetin solution to provoke Heinz-body formation, for Beutler et al. also found that this was much less with primaquine than with acetylphenylhydrazine.

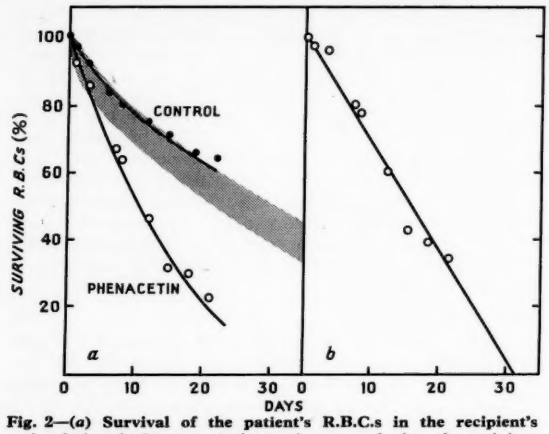


Fig. 2—(*a*) Survival of the patient's R.B.C.s in the recipient's circulation during a control experiment, and when the recipient was taking phenacetin. (The stippled area represents the normal range of disappearance of radiochromium from R.B.C.s); (b) mean cell life of the patient's R.B.C.s when recipient was taking phenacetin (after correction for radiochromium elution).

Glutathione-stability test.—The reduced-glutathione content and the glutathione stability of the patient's R.B.C.s were measured by the methods of Beutler (1957). We found:

Glutathione content = 42·4 mg. per 100 ml. R.B.C.s.

Glutathione content after incubation for 2 hours at 37°C with acetylphenylhydrazine 5 mg. per ml. whole blood = 8·9 mg. per 100 ml. R.B.C.s.

Glutathione stability = 21·0% (normal range 80–100%).

Beutler (1959) found that the glutathione content of all " non-sensitive " subjects remained above 35 mg. per 100 ml. after incubation with acetylphenylhydrazine, whilst that of the " sensitive " subjects usually fell to below 16 mg. per 100 ml. Our result is therefore unequivocally positive, and confirms that the patient is " sensitive ".

Radioactive-chromium Studies

The patient's R.B.C.s were cross-matched with serum from a healthy volunteer of the same blood-group (O, rhesus (D) positive), and another specimen of R.B.C.s was labelled with radioactive chromium and injected into the volunteer's circulation. The life of these cells in the volunteer, estimated by the method of Mollison and Veall (1955), was normal (fig. 2a). A month later the test was repeated, but this time the volunteer recipient took phenacetin 0·5 g. q.i.d. throughout the experiment. The survival of the patient's R.B.C.s was grossly reduced (fig. 2a), and, after correction for radio-chromium elution (Mollison and Veall 1955), the mean red-cell life, in the presence of phenacetin, was 31 days (fig. 2b). 5 weeks after the second injection a careful search was made for antibodies to the patient's cells in the recipient's circulation (by Dr. Fred Stratton of the National Blood Transfusion Service), but none were found.

Discussion

The clinical features and routine laboratory investigations suggested toxic intravascular hæmolysis. Most known causes, except chemical hæmolysis, had been excluded. The only chemicals the patient had taken before admission were compound aspirin tablets. Aspirin and caffeine are not known to produce hæmolysis, whereas phenacetin in large doses is well known to cause chronic hæmolysis. But acute hæmolysis as severe as in the present case, and in response to very small doses of phenacetin, is much rarer. A similar case was described by Sartorelli and Quadrio (1955) in which the patient had taken phenacetin 1 g. before the onset of hæmolysis, but hæmoglobinuria was not recorded. Our patient had had only 0·6 g. of phenacetin when methæmoglobinuria appeared, and because of this we wondered whether he was hypersensitive to the hæmolytic action of phenacetin. Moreover, Dern et al. (1955) showed that phenacetin shortened the red-cell survival-time in patients who had had hæmolytic reactions to primaquine, although they had no patients with phenacetin-induced hæmolysis.

We were able to show, by the in-vitro test of Heinz-body production, that our patient's R.B.C.s were similar to those of the primaquine-sensitive group reported by Beutler et al. (1955a), and this was confirmed by the positive result of the glutathione-stability test. We therefore made radiochromium studies which confirmed our suspicion that phenacetin had caused the hæmolysis.

The mechanism of hæmolysis in patients such as ours differs from that when phenacetin is given in large doses for a long time, when intracellular methæmoglobinæmia appears first, and, if phenacetin therapy is continued, hæmolysis then occurs. Our patient's R.B.C.s were inherently susceptible to chemical hæmolysis, and we believe this is why hæmolysis occurred with such a small dose of phenacetin.

Beutler et al. (1955a) delineated, by their in-vitro test, a group of patients inherently sensitive to primaquine; they later found that the R.B.C.s of most of them had a diminished reduced-glutathione content (Beutler et al. 1955b), and that the reduced-glutathione stability of the R.B.C.s was abnormal in all of them. Glutathione deficiency has been demonstrated also in hæmolysis due to naphthalene (Zinkham and Childs 1957), nitrofurantoin (Kimbro 1957), para-aminosalicylic acid, sulphonamides, and favism (Szeinberg et al. 1957). Gross et al. (1958) suggested that a decrease in glucose-6-phosphate-dehydrogenase activity in the R.B.C.s is responsible for the glutathione deficiency, and they demonstrated this enzymatic abnormality in patients with naphthalene hæmolysis, favism, and hæmolytic anæmia of unknown ætiology; they showed this defect in 7·2% of healthy Negroes and in 1·3% of healthy Caucasians, and suggested, from family studies, a hereditary basis due to a sex-linked and sex-modified gene.

Beutler (1959) has reviewed fully the hæmolytic anæmias associated with this inherent defect in R.B.C.s but most investigations have been made in the United States and Mediterranean countries. The prevalence of the defect in this country is unknown, but we believe that in-vitro tests of Heinz-body production and the measurement of the glutathione stability of R.B.C.s deserve wider application in the study of obscure forms of hæmolytic anæmia.

Summary

A case of acute hæmolysis and methæmoglobinuria was due to a small dose of phenacetin contained in compound aspirin tablets (*B.P.C.*).

The patient, an African, belonged to the group of people whose red blood-cells are inherently sensitive to certain chemicals, including primaquine, phenacetin, acetanilide, and the sulphonamides.

Similar cases may become more frequent in this country now that more people of African ancestry are living here.

Tests for the in-vitro production of Heinz bodies and estimation of the glutathione stability of the red blood-cells are valuable in the investigation of such obscure hæmolytic anæmias.

We should like to thank Sir Robert Platt, Prof. D. A. K. Black, and Dr. M. C. G. Israëls for advice in the preparation of this paper; Sir Robert Platt for allowing us to study the patient who was under his care; and Dr. J. F. Wilkinson for the facilities of the University Department of Hæmatology. We are especially grateful to Dr. C. D. R. Pengelly for the radiochromium studies; to Dr. G. A. Lumb who volunteered to act as recipient for the radioactive red blood-

cells, and to Dr. I. S. Bailey for measuring the glutathione stability. We are indebted also to the members of the Department of Clinical Pathology for their interest and cooperation.

REFERENCES

Beutler E. (1957) *J. Lab. clin. Med.* **49**, 84.
— (1959) *Blood*, **14**, 103.
— Dern, R. J., Alving, A. S. (1955a) *J. Lab. clin. Med.* **45**, 40.
— — Flanagan, C. L., Alving, A. S. (1955b) *ibid.* p. 286.
Dern, R. J., Beutler, E., Alving, A. S. (1955) *ibid.* p. 30.
Fairley, N. H. (1941) *Quart. J. Med.* **10**, 95.
Gross, R. T., Hurwitz, R. E., Marks, P. A. (1958) *J. clin. Invest.* **37**, 1176.
Jasinski, B., Müller, D. (1950) *Schweiz. med. Wschr.* **80**, 681.
Kimbro, E. L. (1957) *Johns Hopk. Hosp. Bull.* **101**, 118.
Marti, H. R. (1958) *Schweiz. med. Wschr.* **88**, 1054.
Mollison, P. L., Veall, N. (1955) *Brit. J. Hæmat.* **1**, 62.
Sartorelli, E., Quadrio, A. (1955) *Med. d. Lavoro*, **46**, 419.
Spaet, T. H., Rosenthal, M. C., Dameshek, W. (1954) *Blood*, **9**, 881.
Szeinberg, A., Sheba, C., Hirshorn, N., Bodonyi, E. (1957) *ibid.* **12**, 603.
Wintrobe, M. M. (1956) Clinical Hæmatology; p. 621. London.
Zinkham, W. H., Childs, B. (1957) *J. clin. Invest.* **36**, 938.

PERICARDIAL BIOPSY

Y. S. BAWA
M.D., F.C.C.P.

M. C. MEHTA
M.B.

P. L. WAHI
M.D.

From the Department of Clinical Medicine, Medical College, Patiala, Punjab, India

THE ætiological diagnosis of pericarditis with effusion, whether isolated or part of polyserositis, often remains obscure, despite many expensive and time-consuming investigations. Differentiation between tuberculous and acute non-specific pericarditis is generally difficult, and delay in diagnosis may seriously affect the final prognosis. In such cases an open pericardial biopsy through an anterior thoracotomy has been recommended (Janovsky et al. 1952, Groves and Effler 1954, Williams and Soutter 1954, Barr 1955, Proudfit and Effler 1956).

This communication describes a simple method of pericardial biopsy with the Vim-Silverman needle, without resorting to open thoracotomy.

Technique

Suitable cases are selected after careful fluoroscopic examination of the chest. It is essential to confirm the diagnosis of pericarditis with effusion and to exclude cardiac dilatation. The biopsy site is in the fifth interspace about 1–1·5 in. outside the left sternal border.

The patient should be sitting against a back rest at an angle of 60–75°. No premedication is required as a rule: the procedure is as simple as pleural biopsy. The biopsy site is anæsthetised down to the pericardium with 2% procaine. A small skin incision is made and an aspiration needle (18 gauge) is introduced for diagnostic aspiration. This is required (*a*) to confirm that the enlarged cardiac shadow is a pericardial effusion and not cardiac dilatation, (*b*) to gauge the distance between the parietal and visceral pericardium (it should not be less than $^1/_2$ in.), and (*c*) to measure the depth at which the fluid is encountered. This depth is marked on the biopsy needle by a clamp.

The biopsy needle with the obturator is introduced slowly through the skin incision till the clamp strikes against the patient's chest wall. The obturator is removed and the cutting needle is introduced so that it has pierced the parietal pericardium. The clamp is removed and the outer needle is advanced forwards about $^3/_4$ in. so that the biopsy shaft is completely covered by the outer needle. Both the shaft and the needle together are rotated through 360°. Sufficient pericardial tissue whirls round the cutting needle, and both the shaft and the outer needle are withdrawn together. The biopsy tissue is contained in the shaft of the cutting needle. The skin incision is closed with a single silk suture.

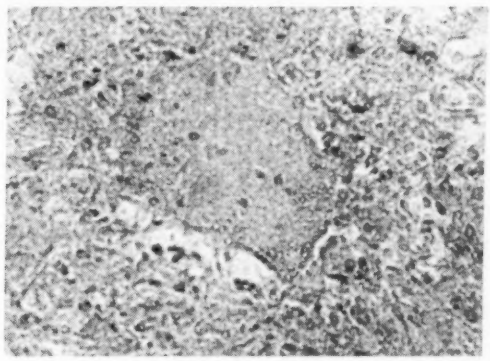


Fig. 1—Typical tuberculous histopathology in pericardial biopsy specimen. (Hæmatoxylin and eosin. ×200.)

Case-reports

Case 1.—A 35-year-old woman was admitted on Sept. 13, 1958, with cough and fever for two months, precordial pain and dyspnœa for ten days, and œdema of the feet for six days. She was in respiratory distress, and her jugular venous pressure was raised. She had ascites, pedal œdema, and pulsus paradoxus. Her temperature was 100°F, and her blood-pressure 105/75 mm. Hg. Her liver was enlarged to three fingerbreadths below the costal margin and it was tender; her area of cardiac dullness was also enlarged. The heart-sounds were normal, but a pericardial friction rub was audible at the base. There were no signs of pleural effusion.

Investigations.—Total leucocyte-count 9800 per c.mm. (polymorphs 84%, lymphocytes 16%), erythrocyte-sedimentation rate (E.S.R.) 58 mm. in the first hour (Westergren), Hb 10 g. per 100 ml., venous pressure 200 mm., Mantoux test positive. Skiagram of the chest showed considerable cardiac enlargement, suggestive of pericardial effusion, and normal lung fields. The electrocardiogram was of low voltage, with generalised T-wave inversion. 150 ml. hæmorrhagic fluid was aspirated from the pericardial cavity: it was an exudate from which no microorganisms were isolated.

Pericardial biopsy was performed on Sept. 19, 1958. Histological examination of the biopsy material revealed areas of caseation surrounded by round cells, epitheloid cells, and giant cells, diagnostic of tuberculous pericarditis (fig. 1).

The patient was treated with isoniazid and streptomycin. She became afebrile within a fortnight and was discharged with E.S.R. of 14 mm.

Case 2.—A 26-year-old man was admitted on Sept. 12, 1958, with cough and fever for three weeks and dyspnœa and dull precordial pain for ten days. He was distressed by orthopnœa and his jugular venous pressure was raised. He

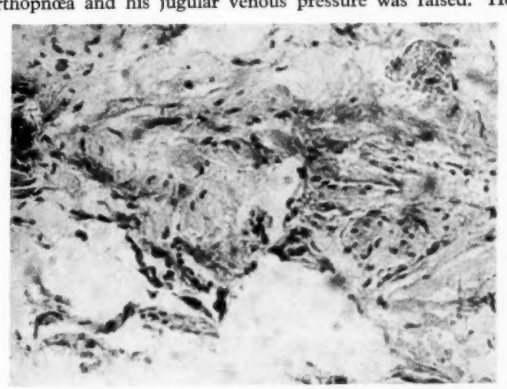


Fig. 2—Pericardial biopsy tissue infiltrated with lymphosarcoma cells (×80).

had ascites and œdema of the feet. His temperature was 100°F, and his blood-pressure 95/70 mm. Hg. His liver was palpable and tender two finger-breadths below the costal margin; his spleen was palpable; and his area of cardiac dullness was enlarged. The heart-sounds were normal but feeble. He had small shotty glands in the neck and signs of pleural effusion on the right.

Investigations.—Total leucocyte-count 18,000 per c.mm. (neutrophils 53%, lymphocytes 46%, eosinophils 1%), E.S.R. 10 mm., Hb 10·7 g. per 100 ml., venous pressure 117 mm., Mantoux test negative. Skiagram of the chest showed considerable cardiac enlargement and a small amount of pleural fluid on the right side. The E.C.G. showed inverted T waves in leads I, AV_L, and V_4–V_6, and flattening of T wave in leads L_{II} and AV_F. 250 ml. fluid was aspirated from the pericardial cavity: it was an exudate which yielded no microorganisms. No definite ætiological diagnosis could be made but the patient was put on salt-free diet and mercurial diuretics parenterally.

Pericardial biopsy was performed on Oct. 12, 1958. The specimen showed collagenous bundles densely infiltrated with hyperchromatic round to ovoid cells with nuclei of various sizes and little cytoplasm. Occasional mitotic figures were also seen. This suggested lymphosarcoma (fig. 2). Subsequent biopsy of one of the cervical lymph-nodes revealed a similar picture.

Case 3.—A 13-year-old boy was admitted on Nov. 11, 1958, complaining of orthopnœa and precordial pain for twenty-five days. He was in respiratory distress, his temperature was 101°F, and he had pulsus paradoxus. His blood-pressure was 90/70 mm. Hg, and his jugular venous pressure was raised. His liver was enlarged three fingerbreadths and his spleen one fingerbreadth below the costal margin; and pea-size lymph-nodes were palpable in his neck and axilla. The precardium was bulging and the area of cardiac dullness was increased. Both heart-sounds were feeble and signs of pleural effusion were present on the left.

Investigations.—Total leucocyte-count 9100 per c.mm. (neutrophils 47%, lymphocytes 50%, eosinophils 3%), E.S.R. 35 mm., Hb 12 g. per 100 ml.; venous pressure 230 mm., Mantoux test negative. Skiagram of the chest confirmed the diagnosis of cardiac enlargement and left pleural effusion. Bloody fluid was aspirated from the pericardial and left pleural cavities: it was an exudate which yielded no organisms on smear or culture. The patient was treated with isoniazid and streptomycin without effect.

Pericardial biopsy was performed on Nov. 26, 1958. The specimen consisted of collagenous bundles infiltrated with hyperchromatic cells—nuclei of various sizes surrounded by narrow rims of cytoplasm. A few mitotic figures were also seen. The picture suggested lymphosarcoma (fig. 3): this was confirmed by cervical lymph-node biopsy.

The patient left the hospital moribund.

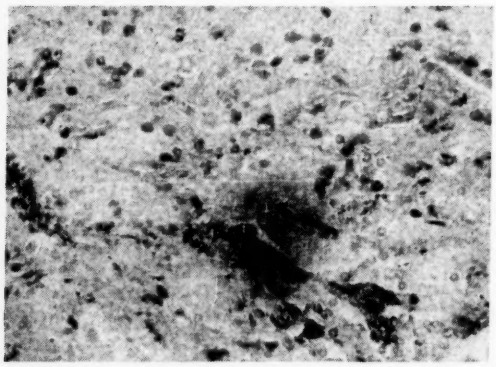


Fig. 3—Pericardial biopsy specimen showing infiltration with lymphosarcoma cells (×200).

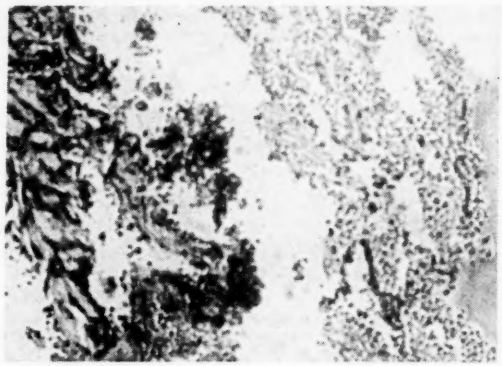


Fig. 4—Pericardial biopsy showing non-specific inflammation (×80).

Case 4.—A 32-year-old man was admitted on Dec. 17, 1958, with a history of orthopnœa and abdominal distension for four months. He was in respiratory distress. His temperature was 98·2°F, he had pulsus paradoxus, and he was slightly cyanosed. His blood-pressure was 100/95 mm. Hg, and his jugular venous pressure was raised. His liver was tender and palpable six finger-breadths below the costal margin. He had pedal œdema and ascites. His area of cardiac dullness was enlarged. His heart-sounds were feeble, and signs of bilateral pleural effusion were elicited.

Investigations.—Total leucocyte-count 3800 per c.mm. (neutrophils 67%, lymphocytes 33%), E.S.R. 7 mm. (Westergren), venous pressure 220 mm., Mantoux test negative. Skiagram of the chest showed bilateral pleural effusions and considerable cardiac enlargement. The E.C.G. showed generalised T-wave inversion and low voltage. About twelve litres of hæmorrhagic fluid from the pericardium, and ten from the right and eight from the left pleural cavities were aspirated during six months' stay in hospital. No microorganisms were cultured or seen on smear. Tuberculosis being the commonest cause of polyserositis in this country, the patient was put on antituberculous treatment, but without improvement.

Pericardial biopsy, on June 6, 1958, revealed collagenous bundles infiltrated with round cells. Most of these were lymphocytes, a few were polymorphs. The picture was suggestive of non-specific inflammation.

The patient left the hospital in despair but was readmitted moribund two months later. He died after four days.

Discussion

Pleural biopsy with the Vim-Silverman or Harefield needle has become established as an easy and fairly reliable method for determining the ætiology of isolated pleural effusions (DeFrancis et al. 1955, Welsh 1958). This prompted us at the beginning of 1958—when we were conducting a study of pericarditis in our unit—to try diagnostic needle biopsy in pericardial effusions.

The 4 cases here reported justified early expectations. In the 1st the diagnosis of tuberculous pericarditis was made possible only by the pericardial biopsy, after all routine investigations had failed. In the 2nd and 3rd our provisional clinical diagnosis had been tuberculous pericarditis, the commonest cause of pericarditis in this country. (Hæmorrhagic fluid is not an uncommon feature in this condition, small, shotty cervical nodes can be tuberculous in origin, and splenic enlargement can be caused by portal venous congestion.) Both these patients were therefore treated for tuberculosis for some time before a pericardial biopsy showed that the true cause of their pericardial effusion was lymphosarcomatous infiltration. Lymph-node biopsy, withheld at first on the

assumption of a tuberculous ætiology, later confirmed the diagnosis. In the last case prolonged streptomycin therapy had produced nerve deafness without improvement of the polyserositis. The pericardial biopsy suggested non-specific inflammation.

We believe that pericardial biopsy in cases of frank pericardial effusion, isolated or otherwise, is a useful and comparatively safe procedure. Its chances of establishing an ætiological diagnosis may be higher than those of pleural biopsy. A further extended trial should prove worth while.

We are grateful to Prof. M. Bala Subrahmanyan, M.D., for the histopathological studies.

REFERENCES

Barr, J. F. (1955) *Arch. intern. Med.* **96**, 693.
DeFrancis, N., Klosk, E., Albano, E. (1955) *New Engl. J. Med.* **252**, 948.
Groves, L. K., Effler, D. B. (1954) *ibid.* **250**, 520.
Janovsky, R. C., Boettner, J. F., Vanordstrand, H. S., Effler, D. B. (1952) *Ann. intern. Med.* **37**, 1268.
Proudfit, W. L., Effler, D. B. (1956) *J. Amer. med. Ass.* **161**, 188.
Welsh, J. D. (1958) *Arch. intern. Med.* **101**, 718.
Williams, C., Soutter, L. (1954) *ibid.* **94**, 571.

Preliminary Communications

REDUCTION OF BLOOD FIBRINOLYTIC ACTIVITY IN DIABETES MELLITUS BY INSULIN

INITIAL tests showed that insulin reduces blood fibrinolytic activity in diabetic patients. We investigated this in more detail; and, since the findings throw light on the spontaneous fibrinolytic activity of blood, the preliminary results are reported.

MATERIAL AND METHODS

Blood fibrinolytic activity was measured in cases of diabetes mellitus by the Fearnley-Lackner method, in which the time of complete lysis of blood diluted in phosphate buffer and clotted with thrombin [1] is recorded photographically.[2] Half-hourly exposures were made on 35 mm. film. Blood-glucose was measured by the method of Folin and Wu.

Newly admitted diabetic patients were studied between 2 and 6 P.M. No insulin was given on the test day before the test, the patients having their usual breakfast and midday meal. A venous-blood sample was obtained at 2 P.M. for determination of blood-clot lysis-time and blood-glucose level. The patient was then given soluble insulin 20 units subcutaneously, and venous-blood samples were thereafter obtained hourly for 4 hours. The glucose levels of the five blood samples were determined shortly after each test was completed.

BLOOD-CLOT LYSIS-TIME AND BLOOD-GLUCOSE LEVELS OF 4 DIABETICS (A-D) BEFORE AND AT HOURLY INTERVALS AFTER SUBCUTANEOUS INJECTION OF 20 UNITS OF SOLUBLE INSULIN

Time (hr.)	A		B		C		D	
	L-T. (hr.)	B.G. (mg. 100 ml.)	L-T. (hr.)	B.G. (mg. 100 ml.)	L-T. (hr.)	B.G. (mg. 100 ml.)	L-T. (hr.)	B.G. (mg. 100 ml.)
0	6	370	8½	290	2	410	3½	520
1	7	290	13½	190	4	250	6	330
2	9½	190	13½	130	5½	210	6	210
3	13	110	7	90	8	150	5	90
4	8½	120	6	100	2½	140	3	130

RESULTS

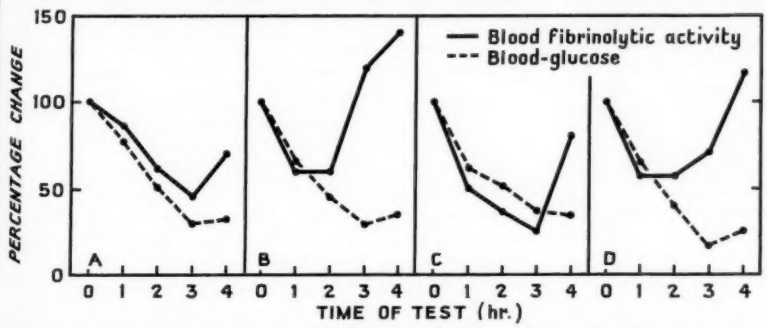
The blood-clot lysis-times and blood-glucose levels of 4 patients (2 male and 2 female) are shown in the accompanying table. The relationship between blood fibrinolytic activity and blood-clot lysis-time is reciprocal; and the percentage changes in blood-glucose level and in blood fibrinolytic activity as a reciprocal function of the clot lysis-time are illustrated in the accompanying figure. This shows that blood fibrinolytic activity fell in conjunction with the fall of blood-glucose level, but that all patients showed a rebound at the third or fourth hour of the tests. 2 of the patients (B and D) who showed the greater rebound experienced mild symptoms of hypoglycæmia, but the other 2 did not.

These results indicate that injection of insulin in diabetes mellitus results in an initial fall of blood fibrinolytic activity in parallel with the reduction of blood-glucose, followed by a rapid rebound when the blood-glucose level is at its lowest.

DISCUSSION

The injection of adrenaline increases blood fibrinolytic activity [3–5]; but how this effect is mediated is unknown. In their effects on carbohydrate metabolism adrenaline and insulin are antagonists, and our results show a fall in blood fibrinolytic activity after insulin followed by a rebound which could well be due to adrenaline release since it corresponded to relative hypoglycæmia.

These results suggest that the spontaneous fibrinolytic activity of blood may be closely connected with and influenced by carbohydrate metabolism. They support the belief that the natural fibrinolytic activity of blood is biologically important.



Percentage changes in blood-glucose level and blood fibrinolytic activity in 4 diabetics after insulin

SUMMARY

In diabetic patients the injection of insulin was followed by a fall of blood fibrinolytic activity in parallel with the fall of blood-glucose. A rebound of blood fibrinolytic activity occurred at low blood-glucose levels; and this rebound is likely to have been caused by adrenaline release.

The data indicate a close connection between blood fibrinolytic activity and carbohydrate metabolism.

G. R. FEARNLEY
M.D. Lond., M.R.C.P.
C. T. VINCENT
M.B. Lond.
R. CHAKRABARTI
M.B. Calcutta

Gloucestershire Royal Hospital, Gloucester

1. Fearnley, G. R., Balmforth, G. V., Fearnley, E. *Clin. Sci.* 1957, **16**, 645.
2. Lackner, H., Goosen, C. C. *Acta hæmat.* 1959, **22**, 58.
3. Biggs, R., Macfarlane, R. G., Pilling, J. *Lancet*, 1947, i, 402.
4. Fearnley, G. R., Revill, R., Tweed, J. M. *Clin. Sci.* 1952, **11**, 309.
5. Fearnley, G. R., Ferguson, J. *ibid.* 1958, **17**, 555.

DIRECT AGGLUTINATION TEST FOR TOXOPLASMA GONDII

SEVERAL serological tests have been employed in the diagnosis of toxoplasma infection. Those in current use include the complement-fixation test.[1 2] Sabin and Feldman [3] observed a new serological reaction in which certain dyes were used to prove the presence or absence of antibody activity in toxoplasmosis (dye test). Recently a hæmagglutinin test which appears to be of practical value was described by Jacobs and Lunde.[4 5] Of these the dye test is probably the one most widely used today. We have employed pure suspensions of *Toxoplasma gondii* in a direct agglutination test for detection of antibodies.

MATERIALS AND METHODS

The virulent RH strain of *Toxoplasma gondii* maintained in cotton-rats was isolated in pure suspension by essentially the same method as that described by Fulton and Spooner.[6] A batch of 20–40 of these animals of 100–200 g. weight, housed singly and inoculated 3 days earlier with 1 ml. peritoneal exudate from a donor animal containing about 20 parasites per microscopic field (4 mm. objective and 6 × eyepiece), were killed by chloroform. The exudate, of average volume 4 ml., was collected by blunt pipette and centrifuged for 15 min. at 2000 *g*. The deposit was resuspended in buffered saline [7] and shaken by hand with glass beads. On standing for a few minutes the majority of the white blood-cells clumped and were removed by pipette. The suspension was then passed through a sintered glass filter of pore size approximately 15–40μ (Baird and Tatlock, 'P3') which was then washed with an equal volume of buffered saline. The parasites, now practically free from white blood-cells, were recovered by centrifugation at 1800 *g* for 5 min. and again suspended in the saline; and the few red blood-cells present were agglutinated by antiserum prepared in rabbits or with addition of guineapig serum to cause hæmolysis in absence of agglutination. The parasites, now free from other cells, were again recovered by centrifugation and resuspended in buffered saline, containing 1% formalin so that the optical density in an 0·25 cm. cell on the 'Hilger Biochem Absorptiometer' without filter was 0·4–0·5. The parasites were kept at 2°C and gently shaken with glass beads before use.

Agglutination patterns: +++, ++, +, and negative from left to right.

For the agglutination test 1 vol. of this material was diluted with 3 vol. formalised saline, and 0·4 ml. was added to a similar volume of serum under test diluted in twofold steps over the range 1 : 10 to 1 : 10,240 at the start. The tubes used were 3 in. by $^1/_2$ in. in diameter and were scrupulously cleaned in chromic acid. The control tube for each row contained saline but no serum. A further tube with serum of previously determined titre was used in each experiment. The tubes were shaken and placed in a water bath at 37°C for 2 hr. They were then left overnight at 2°C and examined next morning with the aid of a mirror on the bench, and the titres of the sera were assessed from the nature of the agglutinating patterns formed.

For the preparation of immune sera in rabbits, and to assess whether the agglutination of toxoplasma by these sera was related to an immune response, three courses of injections were given three times weekly with the sonically disrupted parasites over a period of 6 months. The rise in titre was followed and compared with that found for normal rabbits. The titres of sera from other laboratory animals and from normal and infected patients were also determined.

RESULTS

The agglutination patterns formed in the bottom of the tubes (see figure) were assessed as follows: negative = thick ring; + = thinner ring and carpet; ++ = carpet alone; +++ = carpet with granules and rolled edges.

TABLE I—RANGE OF AGGLUTINATING TITRES FOUND IN THE SERA OF DIFFERENT GROUPS

Group	20	40	80	160	320	640	1280	2560	Total
Children 2–12 yr.	1	1	4	9	8	2	..	..	25
Adults 18–25 yr.	1	..	2	11	9	2	..	..	25
Kala-azar patients	1	1	4	6	7	3	..	1	23

In the rabbit the titre of the serum was found to be 320 and rose steadily to 1600, then 12,800, and finally 81,920 after three courses of injections. After a fourth course the titre was steady one month later at this level. The serum titre of normal cotton-rats and white rats was similar to that for the rabbit.

The range of agglutinating titres found for the sera of different groups of human subjects is shown in table I. The distribution in the first two groups is very similar, with a mean titre value of 160–320. A comparable distribution is found in the patients with kala-azar. This shows that there is no cross-reaction with this infection, which closely resembles toxoplasmosis in so far as multiplication of parasites occurs largely in white blood-cells.

The results of the dye and agglutination tests were compared in 24 sera of high titre. 6 (25%) sera showed no difference in titre, 12 (50%) showed a twofold difference, and 6 (25%) showed a fourfold difference (table II).

These results showed a highly significant correlation ($P < 0{\cdot}001$). With 25 sera of low titre in which dye tests were done in a different laboratory there was no correlation between dye test and agglutination titre ($P < 0{\cdot}10$).

TABLE II—COMPARISON OF THE RESULTS OF DYE TEST AND DIRECT AGGLUTINATION TEST

Agglutination test titre	Dye-test titre						
	512	1024	2048	4096	8192	16,000	>16,000
320	..	2	..	..	..	..	..
640	..	1	..	..	..	..	..
1280	..	1	2	2	..	..	..
2560	..	..	1	3	..	..	..
5120	..	..	..	1	..	2	..
10,240	..	..	..	1	2	..	2
20,480	..	..	..	1	1	1	1

The agglutination titres of another group of 11 sera from patients with glandular fever and positive Paul-Bunnell test were also determined and found to be 640 in 4 cases, and 1280 in 5 cases; 1 had a titre of 2560 and another a titre of 5120. It appears, therefore, that the values were above normal; but the number of tests was too small for any definite conclusions regarding the significance of the findings.

DISCUSSION

In the direct agglutination test of rabbit sera the notable increase in titre which follows immunisation with sonically disintegrated *Toxoplasma gondii* suggests that a true

1. Nicolau, S., Ravelo, A. *Bull. Soc. Path. Exot.* 1937, **30**, 855.
2. Warren, J., Sabin, A. B. *Proc. Soc. Exp. Biol., N.Y.* 1942, **51**, 11.
3. Sabin, A. B., Feldman, H. *Science*, 1948, **108**, 660.
4. Jacobs, L., Lunde, M. N. *ibid.* 1957, **125**, 1035.
5. Jacobs, L., Lunde, M. N. *J. Parasitol.* 1957, **43**, 308.
6. Fulton, J. D., Spooner, D. F. *Trans. R. Soc. trop. Med. Hyg.* 1957, **51**, 123.
7. Krebs, H. A., Eggleston, L. V. *Biochem. J.* 1940, **34**, 442.

immune response is taking place. Since it is the same parasite that infects man the high titres in infected individuals are probably due to the presence of similar antibodies. The range of titres for a healthy population by this test is well below that of those known to be infected. Some degree of specificity is indicated by the fact that the serum titres of those infected with kala-azar, a disease in which the site of development of the parasite resembles that in toxoplasmosis, fall within the normal range. Beverley and Beattie [8] in their investigation on glandular toxoplasmosis have suggested that a dye-test titre below 256 is not significant in this infection. Our values of 160–320 for a healthy population by the direct-agglutination-test agree well with this figure. Our results appear to deviate from those obtained in the dye test of Sabin and Feldman [3] to the same extent as in the hæmagglutination test of Jacobs and Lunde.[4,5] In our experiments, however, the results of dye tests were furnished by other workers. Probably different antigens are involved in the various tests. Our results obtained with sera from 11 cases of glandular fever with positive Paul-Bunnell test show that the titres were slightly raised above those in health.

The direct agglutination of toxoplasma has certain advantages over other serological tests, including the dye test which is the most commonly used test in laboratory diagnosis. The present test is macroscopic and is easy to perform, and dead parasites are used. Reproducible patterns are formed in the bottom of the test-tubes, and many tests can be put up in a short time. The time during which suspension of parasites may be kept has not yet been determined, but we have obtained reproducible results with one suspension after more than six weeks.

8. Beverley, J. K. A., Beattie, C. P. *Lancet*, 1958, ii, 379.

SUMMARY

A macroscopic direct agglutination test for use in the diagnosis of toxoplasmosis gives results comparable with those obtained in the dye-test when sera of high titres are used, is easy to perform, and does not involve the use of live parasites.

It is a pleasure to acknowledge the photographic work of Mr. David Kedgley, of this Institute. We wish to record our thanks to Dr. L. Jacobs, Dr. D. G. Fleck, Dr. G. B. Ludlam, Dr. B. Levin, Dr. S. B. Rosalki, Dr. E. C. D. Taylor, Dr. R. M. Hardisty, and Dr. J. J. Brown for samples of serum; to Dr. P. E. C. Manson-Bahr and Dr. Sen Gupta for sera from kala-azar patients; and to Miss M. V. Mussett for analysing the results.

J. D. FULTON
M.A., M.B. Glasg., D.T.M.
J. L. TURK
M.D. Lond.
National Institute for Medical Research, London, N.W.7

Medical Societies

SOCIETY FOR THE STUDY OF HUMAN BIOLOGY

LAST year this society inaugurated its existence by holding a symposium on Natural Selection and the Evolution of Man, to mark the Darwin centenary. A one-day symposium of this sort is to be an annual event in its calendar, and last week the second was held, on Human Growth.

The proceedings were opened by Prof. A. SCHULTZ (Zürich)—whom Prof. J. Z. YOUNG, in the chair, described as the ideal primatologist, who found his animals in the jungle himself, shot them himself, dissected them himself, measured them himself, and finally drew their bones to illustrate his papers (a record few more strictly human biologists would care to acknowledge, perhaps). Professor Schultz discussed age changes in primates, illustrating how evolution of form so frequently comes about through alterations in the growth-rate of one part of the body compared to others. His data finally—and perhaps sadly, for admirers of *After Many a Summer*—quashed Bolk's concept of man as a fœtalised ape. In respect of some characters, and some only, this concept was true. But in respect of others it could be said that apes were fœtalised men: a study of comparative growth shows more clearly than anything else how relatively early in primate evolution man branched from the common stem, leaving the apes to evolve in their own particular ways.

In the first of two papers from the laboratory of growth and development of the Institute of Child Health, Dr. W. ISRAELSOHN described the raw data of work on human growth and presented curves for various bodily dimensions in children followed for eleven years in the Harpenden Growth Study—records covering the longest age-span of any ever assembled in this country. In emphasising the need for accuracy of measurement, she disclosed the astonishing fact that throughout this study every child has always been measured by the same anthropometrist. She showed how the fitting of mathematical expressions to growth curves can be used to extract the maximum information from such data, and illustrated the point that velocity and even acceleration curves can illuminate the basic processes by showing a slide in which the first appearance of breast growth—the initiation of puberty—occurred at exactly the point of maximal height acceleration in the adolescent growth spurt, and the menarche occurred at exactly maximal deceleration. Dr. J. M. TANNER then discussed the genetics of human growth, presenting the evidence that the age of menarche is to a large extent genetically determined and underlining the existence of a very great genetic diversity in rate of growth and of maturation in man. He described two further gradients of growth impetus in man, in addition to the well-known cephalocaudal one. In the limbs, he said, the peripheral parts are nearer adult status at all stages than the proximal; and in the foot and hand the second phalanges are ahead of the third, fourth, and fifth, which follow in that order. He finally referred to his own and his collaborators' recent work [1] in showing that genes on the Y chromosome are responsible for boys being at all ages, including fœtal life, retarded in maturity compared to girls.

In the afternoon Dr. A. C. STEVENSON took the chair and Dr. D. F. B. ROBERTS, of the anthropology department at Oxford University, described his studies on the growth of tribal African children, emphasising that their lower weight for given height compared to Europeans cannot be solely or even primarily due to malnutrition but is related in some unknown fashion to the climate in which they live—either directly, or genetically through selection.

Mr. A. W. BOYNE, of the Rowett Research Institute of Aberdeen, described the secular trend towards greater size of children—and greater height of adults too—during the past hundred years. Dr. R. M. ACHESON, of Guy's Hospital, showed how this may have come about through better nutrition and less disease. In the children

1. Tanner, J. M., Prader, A., Habich, H., Ferguson-Smith, M. A. *Lancet*, Aug. 22, 1959, p. 141.

of the Oxford Child Health Survey he and his collaborators had found that disease retarded growth in height more than it retarded bone maturation; though these children had not been followed to adulthood, such a finding meant that the disease must necessarily cause a lower adult stature unless the reverse compensation occurs during later years, which was unlikely. His experiments on disease and malnutrition in rats had made him think that the mechanisms of growth slowing involve some reciprocal interaction between cortisol and the secretion of growth hormone.

Finally, Prof. T. McKEOWN, of the department of social medicine at Birmingham University, discussed influences affecting birth-weight, showing how the growth-rate of the fœtus in man—as in the guineapig but not some other animals such as the sheep—slows during the last few weeks before birth, and accelerates again after birth, when the child catches up to its genetically appropriate growth curve. The last few weeks, he thought, are a period of growth potentially fraught with danger in man, and a time upon which perhaps preventive medicine might ultimately be brought to bear.

The papers of the symposium are to be published by the society as a monograph.

Reviews of Books

Arterial Embolism in the Limbs

A. L. JACOBS, M.A., D.M., F.R.C.P., physician, Whittington Hospital, London. Edinburgh: E. & S. Livingstone. 1959. Pp. 200. 35*s*.

THE past ten years have seen true fulfilment follow the early hopes of progress in cardiovascular surgery. Mitral valvotomy and arterial reconstruction have become safe and routine. Meanwhile, the related though far older problem of peripheral embolism seems to have been set aside: a fatalistic attitude to it generally prevails. A more timely contribution than Dr. Jacob's new book on peripheral arterial embolism would therefore be hard to imagine.

He first defines his terms of reference. In order to be more sure of what constitutes evidence of embolism he reviewed the state of the peripheral pulses in 300 patients without evidence of cardiovascular disease. Major pulse deficiencies hardly occurred at all. In 172 patients with mitral stenosis and auricular fibrillation there was significant pulse deficiency in 27·3%. Nearly two-thirds of these gave a history suggesting limb ischæmia at some time in the past, and gradually passing off without lasting disability. The necropsy records of 212 cases of mitral stenosis yielded evidence of previous embolism in about half.

This large and important background to the classical group of cases with acute ischæmia amounting to threatened gangrene is examined critically and the factors tending to make for spontaneous improvement or gangrene are considered. One piece of evidence which will surprise most readers is that the extent of consecutive (propagating) thrombosis in 34 cases examined at necropsy bore no relationship to the fate of the embolised limb. Neither could anticoagulant treatment, or indeed any medical treatment, be shown to have affected the outcome. Physical signs of serious import are waxy pallor and extensive sensory loss. When these last more than two hours the prospect of spontaneous improvement is small.

These are only a few examples of the important conclusions which Dr. Jacobs has been able to draw from his examination of this large personal series. He believes that anatomical factors in the available collateral bed have the greatest influence on prognosis, and wisely adds some advice which surgeons should never forget—that embolism is essentially a complication of serious heart-disease, and that, other things being equal, the rate of perfusion of a limb with arterial occlusion is very much a measure of the cardiac function itself.

This monograph is a model of its kind, and an important contribution to our understanding of a dark corner in the study of cardiovascular disease—not only in its conclusions but also in the way in which these have been reached.

Diseases of Medical Progress

ROBERT H. MOSER, B.S., M.D., major, Medical Corps, U.S. Army; assistant chief, department of medicine, Brooke Army Hospital. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 131. 36*s*.

Major Moser does well to remind us of the many disorders that can be "unintentionally induced as the result of properly indicated, widely-accepted therapeutic procedures". His survey is brief, perhaps too brief, for he seldom gives any indication of the frequency of such unfortunate side-effects. Sulphadiazine and amidopyrine, for example, are listed side by side as possible causes of granulocytopenia with no indication that sulphadiazine is a much less likely offender. In fact, the chief value of the book lies in its bibliography, which runs to 707 references (85% from North American sources), and which forms a useful and salutary record of iatric misadventures. The outlook is sometimes parochial: "Universal acceptance of the coumarin derivatives in the therapy of acute myocardial infarction . . ."; "Virtually every postgastrectomy patient receives a multi-vitamin preparation for a prolonged period of time". Such statements diminish the "global impact".

Nobody Need Be Fat

ROBERT KEMP, M.D., M.R.C.P., physician, Walton Hospital, Liverpool. London: Heinemann. 1959. Pp. 150. 12*s*. 6*d*.

WRITING for both doctors and patients, the author rejects the management of obesity by low-calorie diets. He recommends a system providing a low carbohydrate and a normal fat intake, but a high intake of protein, without reference to the calorie value of the meals. The cost of such a regimen has not been calculated, but Dr. Kemp "would not be surprised to be told that to lose a steady pound a week . . . it might cost . . . at least another pound a week in alternative foods". Analysis of the results of treating 193 patients in this way showed that success could be claimed for a group of 40, with a further 46 still under treatment at the time of writing. These findings and the writings of William Banting are quoted in support of the method. The importance of the writer's enthusiasm in persuading patients to adhere to a system may have been underrated.

Basic Anatomy and Physiology

H. G. Q. ROWETT, M.A., lecturer, Plymouth Technical College. London: John Murray. 1959. Pp. 124. 21*s*.

Miss Rowett is already well known as the author of a number of dissection guides and other books for schools, and this is presumably intended for the same group. It might be read with profit by medical students at the beginning of their courses in these subjects, but its usefulness is limited, since it does not usually give enough detail. As a succinct collection of information on human structure and function for elementary learning it is excellent. The drawings are clear and accurate, and a surprisingly large amount of factual material has been included. On the whole, it instructs, but does not educate. For example, it displays the brachial and lumbosacral plexuses in all their complexity, but gives no explanation of why they exist. It must be questioned whether the whole of the body musculature can be profitably compressed into this sort of book, and whether we should expect such detailed information from the elementary students who could use it. A modicum of biological wisdom, even at the expense of some details (and much could be spared), would greatly improve the value of the book as a means of spreading as widely as possible some understanding of the human body.

THE LANCET

LONDON 12 DECEMBER 1959

Homosexuality and the Law

FOUR years ago we published a Personal Paper [1] in which a senior and widely respected member of a profession described his long unhappiness as a homosexual. Later he wrote, in reply to a critical correspondent: " He seems to start from the assumption that homosexuals are a negligible minority of irresponsible persons interested only in their own selfish gratification . . . I start from the assumption that the majority of homosexuals are responsible and useful citizens ". The article by a family doctor on p. 1077 is a case-study of male homosexuals not as prisoners or patients but as people living an outwardly normal life, whose sexual deviation is unsuspected by most of their neighbours. If the picture of homosexuality is to be seen as a whole, this is part of it.

The main issue now before the public is whether homosexual activity, between consenting adults, need still be treated as a legal crime. In our particular culture, though not in some others, such activity is an offence against the moral code; but offences against the moral code are not necessarily legal offences too. Adultery, for example, is not in this country regarded as a crime. Nor is intercourse with a young girl, provided she is over 16. Prostitution is not in itself a crime. Yet prostitution and seduction and adultery cause untold misery and unhappiness. Families are broken up and thousands of unfortunate children are born each year with a reduced chance of security. The community suffers gravely from these sexual irregularities, and nobody in his senses approves of them. Nevertheless there seemed to be little support for the ARCHBISHOP OF CANTERBURY's recent suggestion—logical in its way—that anti-social behaviour of this kind should be brought within the scope of the criminal law. In our society, the only widely prevalent sexual practice which puts people in danger of prison is male homosexual activity.

Of the total of homosexual offences that presumably take place, only a small fraction—estimated in the Cambridge study [2] at less than 5%—lead to inquiry. In addition, in that investigation, four out of every ten people involved in indictable sexual offences could not be brought to trial, either because they escaped detection or, when detected, could not be proceeded against. Such a state of affairs suggests that the law is not capable of being applied to this branch of human behaviour. On the other hand, where prosecution is undertaken—even unsuccessfully—the penalty can be appalling; and our present system has serious side-effects in blackmail and (often unexplained) suicide. In considering either the fairness or the efficacy of the punishment we should note that sexual proclivities are distributed so that the predominantly homosexual individuals at one end are separated from the heterosexual at the other by an infinite gradation, and that though people may be able to choose what they *do* they cannot choose what they *are*. Though it is doubtful whether a child of normally developing sexuality is likely to suffer lasting harm from seduction, it is all too clear that prison " might almost have been designed as a forcing-ground for young developing homosexuals " [3]. And this is one of the strongest arguments against the use of imprisonment for many of these offenders. It is far more likely to be a hindrance than a help, and its chief justification appears to be the necessity for long-continued preventive detention for those who persistently behave indecently towards children or who repeatedly threaten public order and decency.

To think and talk dispassionately on this subject is oddly difficult; but the attempt can and should be made: as Dr. REDDINGTON said in his letter of Nov. 28, just as the doctor's training should enable him to control his emotion and instinctive reaction when he sees a bad accident, so it should enable him to consider such problems as homosexual behaviour objectively. The Committee on Homosexual Offences and Prostitution [4] set out the facts as it saw them and made important recommendations; and, since the medical profession over the years has provided a great many of these facts, and the problem is as much medical as legal, the public will look to doctors, both individually and corporately, for intelligent comment on the remedies proposed. Though it does not yet seem ready to accept these remedies, its attitude would change the sooner if doctors would take their full part in helping ordinary people to understand the need for change and accept the necessary reforms. For members of the profession wishing to enlarge their own knowledge we know of no clearer summary than the article written at our request by Dr. KENNETH SODDY.[3] On the case for law reform he says:

" In the absence of any rational justification, the retention of male (but not female) homosexuality in the penal code can be explained only as a sop to the primitive and instinctual fears of the community. The responsibility of the homosexual offender for his actions is highly doubtful, for his capacity to control his impulses has often been impaired. There is no evidence that the condition is quantitatively on the increase, and only very doubtful evidence that normal youth can be corrupted by it. At present bad laws are maintained—bad because they cannot be enforced without giving the police intolerable powers of interference with law-abiding citizens. The police are set impossible tasks in proving their charges; and, when convicted, the offender can be sent only to a place which is so unsuitable for him that hope of eventual cure must be abandoned. All this is too high a price for the community to pay for its own primitive fears and feelings."

1. *Lancet*, 1955, ii, 291; see also pp. 346 and 504.
2. English Studies in Criminal Science; vol. IX. London: Macmillan. 1958.
3. Soddy, K. *Lancet*, 1954, ii, 541.
4. Cmnd. 247, 1957. See *Lancet*, 1957, ii, 527.

Sensory Deprivation

FIVE years ago workers at McGill University reported[1] the effects of sensory deprivation in student volunteers who lay in a cubicle on a comfortable bed, wearing frosted goggles to exclude patterned vision, sponge rubber over the ears to reduce sound, and gloves and cuffs to allow free movement but reducing tactile stimuli. Microphones and speakers permitted communication with the subjects. This method, aimed at reducing the patterning of sensory stimuli, has been adopted in further experiments.[2–4] Most subjects found the experience unpleasant: they had difficulty in concentration and directional thought, and some reported visual imagery ranging from simple lines and figures through more complex wallpaper-like patterns to integrated active three-dimensional scenes. A majority recorded visual surface distortions, metamorphopsia, and loss of constancy effects, and there were sometimes persistent after-images. In a few cases these changes lasted for an hour or so beyond the experimental period. Slight changes in other sensory modalities were noted by a few. Most cognitive tests showed a slight decrement of performance under experimental conditions. Electroencephalography revealed changes in the alpha rhythm and the appearance of delta activity during and shortly after the experiment. These various subjective and measured changes, although striking, varied from one subject to another; and the visual disturbances were not true hallucinations, for insight was retained. Other workers, using similar methods, have reported effects of the same sort.[5] LILLY[6] immersed subjects in a tank of slowly flowing water at body temperature, with the aim of reducing the absolute intensity of stimuli and not just the patterning. Others have used tank-type respirators[7]; and SMITH and LEWTY[8] have lately described in these columns their observations on volunteers in a suspended soundproof room. The only negative findings have been reported from a study in which the subjects were in a floating light-proof room but (unlike the condition in most of the other experiments) were allowed to walk about.[9]

This line of study was designed originally for the investigation of "brain-washing".[10 11] In this, sensory deprivation probably does play a part, but it is clearly only one of many factors.[12] ROSENZWEIG[13] has compared the manifestations of sensory deprivation to those of schizophrenia, and the syndrome may, as a model psychosis, be superior to that produced by psychotomimetic drugs. The resemblance, however, is not close; and it is noteworthy that schizophrenics are more tolerant of this procedure than are normals and that in some cases hallucinations are actually reduced.[14] Prof. O. L. ZANGWILL in a lecture last month[15] suggested that the effects were more akin to symptoms due to certain lesions of the cerebral cortex. In newborn animals, he said, sensory deprivation results in learning defects, abnormalities of gait and posture, difficulty in localising painful stimuli, and a sensory abnormality similar to astereognosis—effects which, although temporary, outlast the period of deprivation and seem to be of importance to neurological research.[10 16] Clinically there is very strong evidence that the loss of vision associated with operations on the eye is of prime importance in the psychoses which sometimes follow,[17 18] It has indeed been known since 1863 that placing the cataract patient in a dark room enhances the risk of psychotic disturbance.[18] Advances in operative technique have led to a progressive reduction in the period of bilateral eye-bandaging with a corresponding fall in cataract-psychosis. Similar disturbances have been recorded with poliomyelitis patients in tank-type respirators,[19] and in various clinical states where sensation is cut off—for example, severe sensory polyneuropathies, and extensive injuries or cardiac conditions which require long immobilisation.[20] Sensory deprivation may be one factor in the confusional states of old age, which are usually worse in the dark. A variety of psychiatric disturbances are known to occur in the deaf[21]; deafness and paranoid symptoms have been shown to be significantly related.[22]

Sensory deprivation may be important in accidents due to engine-drivers passing signals set at danger. Evidence has been accumulating that it has a role in road accidents, particularly those associated with long straight highways.[18] Fatigue is known to play an important part; and in experiments on sleep deprivation[23] subjects have had transient disturbances not unlike those obtained with sensory deprivation. MCFARLAND and MOORE[24] have found that American long-haul lorry-drivers, when extremely fatigued, sometimes experience hallucinations and illusions of obstacles on the highway: accidents have occurred as a result of sudden manœuvres to avoid animals or other objects "perceived" on the road. Such hallucinations were reported by no less than 30 of 50 drivers interviewed. Apart from cases where the driver falls asleep at the wheel, the role of fatigue in highway accidents may be subtle and insusceptible to precise measurement. There is no simple relation between hours of driving and accident frequency, for 60% of accidents in truck transport occurred within the first

1. Bexton, W. H., Heron, W., Scott, T. H. *Canad. J. Psychol.* 1954, **8,** 70.
2. Heron, W., Doane, B. K., Scott, T. H. *ibid.* 1956, **10,** 13.
3. Scott, T. H., Bexton, W. H., Heron, W., Doane, B. K. *ibid.* 1959, **13,** 200.
4. Doane, B. K., Mahatoo, W., Heron, W., Scott, T. H. *ibid.* p. 210.
5. Goldberger, L., Holt, R. R. *J. nerv. ment. Dis.* 1958, **127,** 99.
6. Lilly, J. *Psychiat. Res. Rep.* 1956, **5,** 1.
7. Wexler, D., Mendelson, J., Leiderman, P. H., Solomon, P. *Arch. Neurol. Psychiat.* 1958, **79,** 225.
8. Smith, S., Lewty, W. *Lancet*, Sept. 12, 1959, p. 342.
9. Vernon, J., Hoffman, J. *Science*, 1956, **123,** 1074.
10. Hebb, D. O. *Amer. Psychologist*, 1958, **13,** 109.
11. Solomon, P., Leiderman, H., Mendelson, J. H., Wexler, D. *Amer. J. Psychiat.* 1957. **114,** 357.
12. Hinkle, L. E., Wolff, H. G. *Arch. Neurol. Pyschiat.* 1956, **76,** 115.
13. Rosenzweig, N. *Amer. J. Psychiat.* 1959, **116,** 326.
14. Harris, A. *J. ment. Sci.* 1959, **105,** 235.
15. Zangwill, O. L. Lecture, Institute of Neurology, London, Nov. 5, 1959.
16. Hebb, D. O. *Amer. J. Psychiat.* 1959, **111,** 826.
17. Bartlett, J. E. A. *Brain*, 1951, **74,** 361.
18. Ziskand, E. *J. Amer. med. Ass.* 1958, **168,** 1427.
19. Mendelson, J. H., Foley, J. M. *Trans. Amer. neurol. Ass.* 1956, **18,** 134.
20. Leiderman, H., Mendelson, J. H., Wexler, D., Solomon, P. *Arch. intern. Med.* 1958, **101,** 389.
21. Knapp, P. H. *Psychosom. Med.* 1948, **10,** 203.
22. Houston, F., Royse, A. B. *J. ment. Sci.* 1954, **100,** 993.
23. Bliss, E. L., Clark, L. D., West, C. D. *Arch. Neurol. Psychiat.* 1959, **81,** 348.
24. McFarland, R. A., Moore, R. C. *New Engl. J. Med.* 1957, **256,** 792.

three hours on the road. Among other factors are the amount and quality of previous rest, the nature of activities before driving, consumption of alcohol, "accident-proneness", and concurrent emotional stress. But it seems that lack of sensory stimulation during fast driving may be one important, and largely avoidable, element in the causation of accidents. The evidence so far suggests that those of us who drive on such roads as M1 should avoid doing so when fatigued or after taking alcohol; and we may be safer if we travel with a companion or a radio set.

Sacroiliac Arthritis

SACROILIAC arthritis is an invariable feature of ankylosing spondylitis, but is by no means exclusive to that disease. The sacroiliac joints form a focus of interest to students of several diseases not otherwise obviously related. Thus the venereologist finds these joints involved in some cases of Reiter's syndrome, the dermatologist in a few patients with psoriasis and arthritis, and the gastroenterologist in some cases of ulcerative colitis. Moreover the ophthalmologist recognises the link between diseases of the eye and of the sacroiliac joints in ankylosing spondylitis and in Reiter's syndrome. The interrelation of these diseases was discussed last year by the Medical Society for the Study of the Venereal Diseases, and the proceedings have been published in the *British Journal of Venereal Diseases*.

Of the diseases commonly associated with sacroiliac arthritis, ankylosing spondylitis and Reiter's syndrome have the greatest number of manifestations in common; but these two diseases differ in several important respects. Generally speaking the sacroiliac joints are affected early in ankylosing spondylitis and rather later in Reiter's syndrome. The overall incidence of sacroiliitis in Reiter's syndrome has been estimated as from 20% to over 30%, rising to 54% in cases of more than six years' duration.[1–3] Spondylitis is not common in this disease, and lesions of the central joints are much less important as a cause of symptoms and disability than are those of peripheral joints, particularly of the lower limbs. Iritis, plantar fasciitis, and severe lesions of peripheral joints are much commoner in Reiter's syndrome when sacroiliitis is present than when it is not. GRAINGER and NICOL [4] find that on radiographic examination unilateral involvement or lack of symmetry are commoner in Reiter's syndrome than in ankylosing spondylitis. Periostitis, particularly of the under-surface of the os calcis, is usually more florid in Reiter's syndrome, and keratoderma and balanitis circinata do not occur in ankylosing spondylitis. As GRAINGER and NICOL point out, the radiographic changes of ankylosing spondylitis may be confined for several years to the sacroiliac joints, and it may be impossible to diagnose precisely the disorder in a patient with bilateral sacroiliac arthritis, calcaneal erosions, anterior uveitis, and an unobtrusive urethral discharge.

1. Csonka, G. W. *Brit. J. vener. Dis.* 1959, **35**, 77.
2. Mason, R. M., Murray, R. S., Oates, J. K., Young, A. C. *Brit. med. J.* 1958, i, 748.
3. Oates, J. K. *Brit. J. vener. Dis.* 1958, **34**, 177.
4. Grainger, R. G., Nicol, C. S. *ibid.* 1959, **35**, 92.

The last of these symptoms is a reminder that gonococcal infection (not then differentiated from non-specific urethritis) was once commonly held to play a part in the pathogenesis of ankylosing spondylitis. This hypothesis is now not widely held, but there seems no doubt that chronic prostatovesiculitis is common in ankylosing spondylitis: frequencies as high as 98%,[5] 83%,[2] and 84%[6] have been cited. A similar chronic infection has been found in 17–35% of normal men, and in 33% of male patients with rheumatoid arthritis.[2] Nobody has been prepared to claim that this chronic infection is a causal factor in the disease (which often starts before puberty and in which a genetic factor is known to operate), and the difficult task of testing the therapeutic effect of eradicating it has yet to be tackled.

Urethritis is of course an integral part of acute Reiter's syndrome and may be followed by symptomless chronic prostatitis—invariably present in chronic relapsing cases. GRAINGER and NICOL [4] speculate on a possible link between pelvic infection and sacroiliac arthritis in ulcerative colitis (a disease in which BYWATERS and ANSELL [7] found the sacroiliac joints affected in 6 out of 37 cases) and in paraplegia.[8 9] The association of Reiter's syndrome with dysentery is well known, though in this country, for some unknown reason, urethritis is much the more common accompaniment. Pelvic infection has not been reported in cases where the radiographic changes of ankylosing spondylitis are found in patients with psoriasis,[10–14] but this may not have been specifically sought. To complete the list of diseases in which non-suppurative sacroiliac arthritis has been found we may add rheumatoid arthritis (sacroiliac arthritis was present in 10% of MASON'S [2] cases of rheumatoid arthritis) and the rare type of chronic arthritis thought to be due to recurrent rheumatic fever.[14 15]

The characteristic ophthalmic lesion of ankylosing spondylitis is unilateral non-granulomatous anterior uveitis, present in 13—25% of all cases [16 17] and in a higher proportion of those of long duration or with arthritis of peripheral joints. Conjunctivitis is the classical finding in Reiter's syndrome, but iritis has been observed in 6–30%.[18–20]

Of all the syndromes in which sacroiliac arthritis is known to occur, Reiter's syndrome seems the most likely to be due to a specific infective agent, though this has hitherto eluded detection. It seems unlikely that the same agent plays a part in other syndromes in which sacroiliac arthritis is the main common feature; but the possibility provides a stimulus to those who seek to identify it.

5. Romanus, R. *Acta med. scand.* 1953, **145**, suppl. 280.
6. Oates, J. K. *Brit. J. vener. Dis.* 1959, **35**, 89.
7. Bywaters, E. G. L., Ansell, B. M. *Ann. rheum. Dis.* 1958, **17**, 169.
8. Abramason, D. J., Kamberg, S. *J. Bone Jt Surg.* 1949, **31A**, 275.
9. Abel, M. S. *Radiology*, 1950, **55**, 235.
10. Sherman, M. S. *J. Bone Jt Surg.* 1952, **34A**, 831.
11. Sterne, E. H., Schneider, B. *Ann. intern. Med.* 1953, **38**, 512.
12. Fletcher, E., Rose, F. C. *Lancet*, 1955, i, 695.
13. Wright, V. *Ann. rheum. Dis.* 1956, **15**, 348.
14. Sharp, J. *Brit. med. J.* 1957, i, 975.
15. Bywaters, E. G. L. *Brit. Heart J.* 1950, **12**, 101.
16. Hart, F. Dudley. *Ann. rheum. Dis.* 1955, **14**, 77.
17. Wilkinson, M., Bywaters, E. G. L. *ibid.* 1958, **17**, 209.
18. Zewi, M. *Acta ophthal., Kbh.* 1947, **25**, 47.
19. Paronen, I. *Acta med. scand.* 1948, **131**, suppl. 212.
20. Ford, D. K. *Ann. rheum. Dis.* 1953, **12**, 177.

Annotations

A GUIDE TO GIVING

To give is more blessed than to receive; but, whatever their ratio of beatitude, both acts have their difficulties and cannot be practised effectively without wisdom and discrimination. Some of the problems of contemporary donors and recipients were discussed last week by Mr. Leslie Farrer-Brown, director of the Nuffield Foundation, in his Birkbeck College Foundation oration. His theme was Dispensing Bounty, and as servant of a charitable trust he spoke as a craftsman on the complex art of giving.

For the donor the chief difficulty is choice—choice of subject, choice of men, choice of policy. Mr. Farrer-Brown described a grant as an act of faith in the "worthwhileness" of the purpose for which the money was given. How to determine what was worth while was the "elemental" problem. He approved the view of John D. Rockefeller that "money is a feeble offering without the study behind it which will make its expenditure effective", but added that too much preparatory study could paralyse the will to act. He agreed, however, that dispensers of bounty should learn as much as they could about the subjects in which they were interested, and, even more important, about the people they might be able to help. Knowledge could at least reduce the uncertainties, offer protection against the wiles of the cadger, and on occasion, by suggesting unsuspected possibilities, widen the field of choice. In the pursuit of knowledge the dispensers of bounty must at times be remote, viewing the philanthropic scene from afar, but they must also be "out and about in the market place", making their own judgments of people and trends. They should be, as Mr. Farrer-Brown put it, "keen in their assessments, but no less persistent in their appetite for excellence". Without expert advice they could not go far, but the responsibility for decision must rest with them.

Most important of all, they must decide how much an enterprise mattered to its promotors; for, in his experience, "a project manufactured without passion was rarely worth supporting". But the dispensers of bounty must themselves bring warmth and sympathy to their choice, for too dispassionate dispensation could blight enthusiasm. He preferred close continuous relations, such as universities maintained with the University Grants Committee, to the often sporadic contacts of private bounty. But in the last resort dispensers of bounty must reach their final choice by tutored guesswork. How else, he asked, could one decide such questions as:

> "Whether to spend more money on research on rheumatism, where, for the present, the problems are frustrating, or instead, to spend on genetical studies of wild populations of butterflies and snails, knowing that this work already promises to contribute to medical knowledge: whether to spend on the improvement of hospitals or on trying to discover more certain knowledge about social relations and conditions suspected of contributing to ill-health; or whether to support the study of criminals or of the development of behaviour in the very young, both topics on which very little valid information exists. Should one spend on the young or on the care of the aged; spend at home or in the underdeveloped countries, and if the latter, on, say, the control of disease, or the increase of food production, both pressing needs?"

In discussing the problems of donors Mr. Farrer-Brown naturally drew on his own experience. As representative of the recipients he chose the universities because for centuries they have lived successfully on bounty from State, Church, Merchant, and Patron. Today they were almost entirely dependent on the bounty of the State, but they still derived a small part of their income from contemporary versions of their other traditional sources of income. This unofficial supplement Mr. Farrer-Brown considered of inestimable value, for it allowed a measure of intramural nonconformity and extramural independence. Though the Universities Grants Committee respected the individuality of their charges, they must strive to be fair to all and therefore must often apply standard measures. If a university wanted to try something unorthodox or was convinced of the value of better standards of, say, staffing or building, with help from a body free from the obligation to make equivalent provision for all, it might experiment or indulge its special conviction. But Mr. Farrer-Brown added the warning that much of the value of these private grants as contributions to freedom and variety of action would be lost unless the universities in spending them were allowed to disregard official standards.

Even though they need money badly, the universities are sometimes discouraged by the spirit in which it was offered. Even State Bounty, Mr. Farrer-Brown thought, was partly prompted (in the words of the principal of Glasgow University) by the desire not so much for "more knowledge, as more power, more devices, more machines". But, though sympathetic to these academic scruples and doubts, Mr. Farrer-Brown was on the whole hopeful. The universities had successfully grappled with similar problems throughout history. The present hectic interest in scientists and technologists could be matched by an earlier dominant interest in the number and training of the clergy. He thought that already he discerned signs of a reaction from technology and of increased bounty for the creative arts, and he wondered whether, having paid so much attention to quantity, the time had not come when we should pay more heed to quality. The past had produced King's College Chapel, Cambridge. "What equally grand and lovely things", he asked, "are we of this generation producing in our universities for the enrichment and inspiration of ourselves and our successors? Is it not time that the universities and the dispensers of bounty determined together to 'make the peaks higher', to make the good things finer, to bring some splendour to our utilitarian age?"

RHEUMATOID FACTOR AND INHIBITOR

In 1956 Ziff et al.[1] showed that normal sera contain a substance capable of inhibiting the agglutination of sensitised sheep cells by serum from patients with rheumatoid arthritis. They found that this inhibitory substance was deficient in rheumatoid sera, and claimed that its absence was a more sensitive indication of rheumatoid arthritis than the presence of the agglutinating factor itself. Although attempts by others to repeat this work have failed to confirm the high diagnostic value of the Ziff test, the presence of inhibitor in normal sera is now well established. The presence of a similar inhibitory substance in certain tissue-extracts has now been reported by Gray.[2]

Changes in the villi of the placenta of women undergoing spontaneous abortion are somewhat similar to those in the connective tissues in some "collagen" diseases. In consequence Gray determined the differential agglutination titre (D.A.T.) in a group of such women and found the figures significantly higher than those from the

1. Ziff, M., Brown, P. C., Lospolluto, J., Badin, J. *Amer. J. Med.* 1956, **20**, 500.
2. Gray, J. D. *J. Immunol.* 1959, **83**, 1.

controls. An extract of normal human placenta was found considerably to reduce these titres when added to the sensitised sheep cells used in the tests. In consequence Gray extended his investigations to other tissues and found considerable inhibitory activity in all the tissues studied—namely, heart-muscle, lung, liver, placenta, and kidney in decreasing order of potency. These extracts moreover were equally active against high-titre sera from patients with rheumatoid arthritis. Various tests suggest that the tissue inhibitor is a protein (probably a globulin) and that its action is directed against the agglutinating factor and not against the sensitised cells. An interesting property of this tissue inhibitor is its thermolability: two hours at 57°C resulted in complete loss of activity. Since normal serum is known to contain considerable amounts of inhibitor, the low D.A.T. given by normal sera may conceivably be due in part to such inhibitors. The striking rise in agglutinating titre brought about by heating normal sera for two hours at 57°C not only supports this hypothesis but also strikingly emphasises the similarity between tissue and serum inhibitors.

As a result of these and related observations Gray suggests that the relation of the rheumatoid factor to tissue inhibitor is that of antibody to antigen or hapten. Since, however, both are demonstrable in the serum of healthy people, the abnormality in rheumatoid arthritis is deficiency of antigen vis-à-vis antibody—which is the converse of the state in health. Whether this is due primarily to excess of the factor or deficiency of inhibitor is still undertermined. If the material responsible for the agglutinating activity found in normal sera after two hours' incubation at 57°C is indeed identical with the rheumatoid factor, then this factor is not (as has been believed) almost uniquely associated with rheumatoid disease; and if indeed the rheumatoid factor is an antibody to altered γ-globulin [3 4] the production of such an antibody must be regarded as a normal function of healthy individuals. But before such a conclusion can be accepted, more convincing evidence of the identity of these agglutinating factors will have to be found.

STANDARDS FOR WEIGHT AND HEIGHT IN INFANTS AND CHILDREN

In this country we have been slow to recognise that the rate of growth of children provides a valuable index of the public health, and that social-class differences in weight and height may reflect more accurately than most other measures the rise or decline of the barriers of class. The public-health authorities in Canada and Yugoslavia, to take but two examples, have conducted extensive surveys of the physical development of their youth, and plan to repeat these periodically. Our own Ministry of Health, though it supports the excellent Harpenden growth study—a small longitudinal investigation whose techniques and results have exerted considerable influence throughout the world—has not till lately itself engaged in survey work. At the request of the British Pædiatric Association, a survey of children's weights was begun in 1949–50, and the first results have now appeared.[5]

The survey, planned longitudinally over the three years after birth, deals with some 17,000 healthy children, measured at welfare clinics in urban and rural districts all over England and Wales. Though nearly half the children had failed to continue attending by the end of the first year, two-thirds by the end of the second year, and four-fifths by the end of the third, the numbers and representativeness are still a great improvement on those in previous studies. Much interesting information has been brought to light. Average birthweights are 7·53 lb. for boys and 7·21 lb. for girls, but firstborns average 0·2 lb. lighter than second, and second 0·1 lb. lighter than third and subsequent children. Firstborns, like all small infants, grow faster than others during the first six months and the difference is wiped out by the end of the first year. Birthweight differences between the social classes are small, being now only 0·2 lb. between the top managerial and lowest unskilled labouring. No difference could be detected between weight gains of infants with health records marked excellent, average, and poor, indicating how great is their ability to recover from childhood ailments. The main point of the survey, however, was to provide standards for use by welfare clinics, pædiatricians, and practitioners. These standards are presented, for boys and girls separately, in terms both of weight attained at each week of age from birth to 3 years and of weight gain per each three months in this period. In each case the average is given, together with a "normal" range, this being the 5th to 95th percentiles. As these graphs are not very practical for use in the clinic, it is a considerable relief to discover that they coincide closely with the new standards for weight and height recently published by Dr. Tanner and Mr. Whitehouse, which are referred to in a letter on p. 1086 of this issue.

These standards cover the whole age range from birth to maturity in three overlapping sections and enable the user to place a child approximately at his nearest 5th percentile among the population. Doubtless they will soon be out of date, for all the evidence indicates that the secular trend towards larger size for a given age is still continuing in Western Europe, America, and Japan. But at least we have standards based on British children available now. It is to be hoped that periodic full-scale surveys will keep them up to date.

AMINE IN SEARCH OF A FUNCTION

The literature on 5-hydroxytryptamine (5-H.T.) seems to have reached its logarithmic phase of growth. Page listed 153 references in 1954,[1] but 529 last year.[2] The first issue of a new journal, *Medicina Experimentalis*,[3] in which three of the eleven articles are devoted to some aspect of 5-H.T., reflects this trend.

One of these papers, by Laborit et al.,[4] draws attention to no less than three new and rather exotic properties of the amine.[5–7] Pretreatment with 5-H.T. was found to protect mice against the convulsions which supervene when they are exposed to oxygen at increased pressure. This shielding effect probably stems from the vasoconstrictor action of 5-H.T., with consequent restriction in tissue-oxygen supply. It is reminiscent of the radioprotective action of 5-H.T., which may be due to a similar mechanism.[8] The second claim—that 5-H.T. has an auxin-

3. Glynn, L. E., Holborow, E. J., Johnson, G. D. *Proc. R. Soc. Med.* 1957, **50**, 469.
4. Edelman, G. M., Kunkel, H. G., Franklin, E. C. *J. exp. Med.* 1958, **108**, 105.
5. *Rep. publ. Hlth med. Subj., Land.* 1959, no. 99.

1. Page, I. H. *Physiol. Rev.* 1954, **34**, 563.
2. Page, I. H. *ibid.* 1958, **38**, 277.
3. *Medicina Experimentalis.* Edited by Prof. R. Domenjoz, University Institute of Pharmacology, 2b, Reuterstrasse, Bonn, Germany. Published by S. Karger, Ltd., 25, Arnold-Böcklin Strasse, Basle, Switzerland. Subscription Sw. fr. 56 per volume of six issues (two vols. annually).
4. Laborit, H., Niaussat, P., Broussolle, B., Jouany, J. M. *Med. exp.* 1959, **1**, 27.
5. Laborit, H., Broussolle, B., Perrimond-Trouchet, R. *C.R. Soc. Biol., Paris*, 1957, **151**, 930.
6. Niaussat, P., Laborit, H., Dubois, C., Niaussat, M. *ibid.* 1958, **152**, 945.
7. Laborit, H., Jouany, J. M., Niaussat, P. *ibid.* 1959, **153**, 549.
8. van den Brenk, H. A. S., Moore, R. *Nature, Lond.* 1959, **183**, 1530.

like action approaching that of indoleacetic acid—is rather surprising and needs confirmation; for even 5-hydroxy-indoleacetic acid, which only differs from the natural auxin, indoleacetic acid, by possessing a hydroxyl group, has but 6% of its ability to influence plant growth.[9] The third claim of Laborit et al.—that administration of pituitary growth-hormone to the rabbit causes an increased urinary output of the 5-H.T. metabolite, 5-hydroxy-indoleacetic acid—must be treated with even greater reserve, for it conflicts with the findings of other workers [10 11] that production of this metabolite is not an important metabolic pathway in herbivores.

These three putative pharmacological responses form but a small proportion of the bewildering number of properties of 5-H.T. that have been educed in the artificial conditions of the laboratory. To relate them to the physiological role of 5-H.T. in the intact organism is quite another matter. Despite prodigious experimental effort, the function of 5-H.T. still remains largely unknown. Many of the early claims, such as its supposed influence on hæmostasis or diuresis, have not been substantiated.[2] Possibly 5-H.T. is even biochemically atavic, with no function, although its widespread biological distribution and high pharmacological activity suggest that this is unlikely. Indeed, some areas of investigation begin to show promise. The elegant experiments of Bülbring and Lin,[12] for instance, suggest that 5-H.T. may be a local tissue hormone, important in the maintenance of normal gut motility. Even the plethora of psychiatric speculation (reviewed by Himwich [13]), much of it based on rather exiguous evidence, cannot mask the fact that 5-H.T. is probably of importance for the normal functioning of the central nervous system.[14] Though no explanation is immediately forthcoming to account for the presence of 5-H.T. in such diverse sites as tomato pulp [15] or the sting of the scorpion,[16] the future is not unhopeful: already we know rather more about 5-H.T. than we do about histamine, which has been studied for many years longer.

ATYPICAL MYCOBACTERIAL INFECTIONS

THE atypical mycobacteria associated with pulmonary disease in man resemble tubercle bacilli in some ways but in other ways are more like saprophytic acid-fast bacilli. The general impression seems to be that these mycobacteria have become commoner,[17] and certainly they have been reported more frequently since the use of anti-tuberculous drugs has become widespread. There is a good deal of disagreement about their relation to tuberculosis: some dismiss them as contaminants while others regard them as true causes of disease.

Selkon and Mitchison[18] have found that of 1081 patients with newly diagnosed and previously untreated tuberculosis associated with positive cultures, 55 yielded strains which were resistant to streptomycin, *p*-amino-salicylic acid, and isoniazid. Of these 55 strains, 7 were found to be atypical mycobacteria. Selkon and Mitchison used both in-vitro and animal-virulence tests. In the first group, the tests included bacillary morphology, colonial morphology on Löwenstein-Jensen and oleic-acid albumin agar media, pigmentation, cord formation, growth in ' Tween '-albumin liquid medium at 22° and 37°C, growth at 37°C on Löwenstein-Jensen medium and on tryptic-digest agar medium, catalase activity, arysulphatase activity, methylene-blue-reduction time, niacin tests, neutral-red tests, thiosemicarbazone-sensitivity tests, fermentative activity, heat resistance, and ability to grow at 45°C on Löwenstein-Jensen medium. The animal-virulence tests consisted of inoculation into guinea-pigs, rabbits, and mice. The three most valuable in-vitro identification tests proved to be the study of colonial morphology on oleic-acid albumin agar plates, the niacin test, and the thiosemicarbazone-sensitivity test. Their work shows clearly that for the certain identification of some of these strains much painstaking investigation is required.

Lewis et al.[19] report a more extensive survey of acid-fast organisms isolated in Florida in the three years from 1955 onwards. 215 patient-strains of atypical mycobacteria were identified; but the report is concerned with the first 100 consecutively studied patients from whom atypical mycobacteria were isolated in the Florida State tuberculosis hospitals. Each of these 100 strains differed from *Myco. tuberculosis* in several respects. They grew at room-temperature and they failed to form tightly woven cords in liquid medium. 96 showed catalase activity greater than that of *Myco. tuberculosis*, and the remaining 4 showed equal catalase activity. The strains could be classified by their ability to produce pigment when grown in continuous light and in total darkness. Three major groups were distinguishable: the photochromogenic organisms, which produced yellow pigment when grown in the presence of light, and white or buff-coloured colonies when grown in the dark; the non-chromogenic organisms, which produced white, buff, or yellowish pigment both in the light and in the dark; and the scotochromogens, the majority of which produced the same degree of yellow-orange pigment whether grown in the light or in the dark. Of the 100 strains, 7 fell into the first group, 78 into the second, and 15 into the third.

Lewis et al. point out that infections with these organisms were discovered in 2% of the patients in the State tuberculosis hospitals; and in 74% of these patients they appeared to be definitely the cause of pulmonary disease. In the remaining 26% there was either bacteriologically proved tuberculosis or only a single growth of atypical mycobacteria, which might therefore be dismissed as contaminants. These workers found no evidence that the atypical mycobacteria could cause contagious infection, but they could not exclude transmissibility from man to man. The disease produced by these organisms could not be distinguished clinically, pathologically, or radiographically from tuberculosis and could be properly diagnosed only by careful bacteriological study. The prognosis is worse than that of tuberculosis since most of these organisms are resistant to antituberculous drugs.

It seems fairly certain that a good deal more will be heard about these interesting organisms. Distinction of atypical mycobacteria from drug-resistant mutants of true tubercle bacilli is by no means easy. Nor is it easy, even when the distinction has been made, to explain their origin. Possibly they represent a rare type of mutant which can arise in strains of ordinary tubercle bacilli but which (like drug-resistant mutants) would not have been detected easily in the absence of chemotherapy. Certainly it would be disastrous if true tuberculosis were to be eliminated only to be replaced by a false tuberculosis less amenable to treatment by drugs.

9. Ek, A., Witkop, B. *J. Amer. chem. Soc.* 1953, **75**, 500.
10. Erspamer, V. *J. Physiol.* 1955, **127**, 118.
11. Nakai, K. *Nature, Lond.* 1958, **181**, 1734.
12. Bülbring, E., Lin, R. C. Y. *J. Physiol.* 1958, **140**, 381.
13. Himwich, H. E. *Science*, 1958, **127**, 59.
14. Gaddum, J. H. *Int. Congr. Physiol.* 1956, **1**, 442.
15. West, G. B. *J. Pharm. Pharmacol.* 1958, **10**, 589.
16. Adam, K. R., Weiss, C. *J. exp. Biol.* 1958, **35**, 39.
17. See *Lancet*, 1959, i, 1266.
18. Selkon, J. B., Mitchison, D. A. *Tubercle, Lond.* 1959 **40**, 141.
19. Lewis, A. G., et al. *Amer. Rev. resp. Dis.* 1959 **80**, 188.

Conferences

ALCOHOLISM AND HEPATIC CIRRHOSIS

A MEETING on alcoholism and cirrhosis of the liver was held in New York on Nov. 20 and 21 under the presidency of Dr. HANS POPPER (New York) and under the auspices of the National Council on Alcoholism. Cirrhosis is now the fifth commonest cause of death in the United States. It was estimated that one in sixteen of those who take alcohol becomes an alcoholic and about 8% of these will develop cirrhosis.

C. H. BEST (Toronto) believed that the basis of the relation between the two was a nutritional one. A precirrhotic fatty-liver stage could be induced in rats by giving, for about a year, a diet containing 15–30% of calories as alcohol. This change could always be prevented by choline or methionine. G. KLATSKIN (New Haven) noted that, in rats, alcohol reduced the food intake and increased the requirement for choline. Alcohol could induce fatty change irrespective of calories consumed, and this was reversed by choline. The lesion in the liver of the rat, however, differed from that seen in man: inflammation and degenerative changes in the liver cells were absent. He speculated whether there might not be an additional factor in the human disease, perhaps a direct "toxic" effect, perhaps additional infection.

The mechanism of fatty liver in alcoholics was further discussed. W. S. HARTROFT (St. Louis), by electron microscopy, had noted that in the fatty liver produced by excess calories the fat was periportal in distribution and situated in little orgastoplasmic saccules, whereas in choline deficiency the fat was centrizonal and the mitochondria were enormous. In choline deficiency the mitochondria might be unable to wrap around the fat globules with possible interference with oxidative enzymes on the surface of the mitochondria. J. H. QUASTEL (Montreal) had studied the effect of alcohol on isolated liver tissue and found an inhibition of phospholipid production and a stimulation of fatty-acid synthesis. C. S. LIEBER (Boston) had incubated trace amounts of ^{14}C-labelled acetate or ethanol with rat liver slices. Both served equally well for fatty-acid synthesis although far more fatty acid was found with ethanol than with acetate. He believed that ethanol acted as a donor of hydrogen ions reducing dipyrridine phosphate (D.P.N.). H. M. MALING (Bethesda) related the acute experimental fatty liver after alcohol to altered fat transport, the fatty acids coming from depot adipose-tissue.

The incidence of cirrhosis parallels the consumption of alcohol in a community, but less than 10% of alcoholics develop liver injury. The cause of the individual susceptibility is not known. W. S. HARTROFT emphasised the importance of preceding obesity. F. SCHAFFNER (New York) found a four times greater incidence in white than in the coloured patients seen at Cook County Hospital, Chicago. C. M. LEEVY (Jersey City) observed a higher incidence in those presenting with delirium tremens, 25% of whom showed cirrhosis and 30% fatty change.

The usual cirrhosis in alcoholics is a fine Laennec's one (about 80%). It was agreed, however, that about 8% show a coarse postnecrotic type of lesion and 10% a mixed picture. The association of alcoholism with hæmochromatosis was stressed, 2% of cirrhosis in alcoholics being of this type. The transition of Laennec's to postnecrotic cirrhosis has been described both in animals and by serial needle biopsies in man. This transition is liable to occur if the alcoholic abstains and large nodules regenerate in the liver. The liver cells in alcoholism contain basophilic amorphous material, the Mallory bodies. H. POPPER had seen these in both the Laennec and postnecrotic cirrhosis developing in alcoholics but never in non-alcoholics. P. E. STEINER (Philadelphia), on the basis of studies in Africans, disagreed; for he found Mallory bodies very frequently in the absence of alcoholism and even of fat in the liver cells.

R. M. KARK (Chicago) had seen severe fatty change and ascites disappear in alcoholics given a good diet, and it was generally agreed that this was true of other acute changes in the liver such as polymorph infiltration; fibrosis could diminish. S. SHERLOCK (London) believed that once the architecture of the liver was disturbed anatomical restitution was impossible. C. S. DAVIDSON (Boston) emphasised the distinction between the acute changes (with fat, necrosis, inflammatory cells and Mallory bodies, and clinically liver failure) and the chronic burnt-out stage (with mainly fibrosis and clinically the development of portal hypertension). The improvement in an alcoholic who gave up alcohol and took a normal diet was so great that every effort should be made both to secure early diagnosis—which may necessitate needle liver biopsy—and to ensure continued abstinence.

Special Articles

MALE HOMOSEXUALITY

BY

A MEDICAL PRACTITIONER

A TRUE picture of male homosexuality in the community cannot be given if—as in most medical publications—it is based on material drawn only from psychiatric practice, prisons, mental hospitals, and venereal-disease clinics. So long as the only doctors who write on this subject are heterosexual, so long as public opinion is based on emotional prejudice, so long as the law makes it dangerous for the homosexual himself to express an opinion, the present profound ignorance of the subject—both inside and outside the medical profession—will continue.

As a general practitioner and a homosexual, I have over the past thirty years discussed the subject intimately in an atmosphere of mutual understanding and confidence with several hundred homosexual men of many nationalities, colours, cultures, and creeds. The following case-histories provide, I believe, a typical cross-section of male homosexuality in the community.

Case-histories

Cases 1 and 2.—In 1935 A was a contented married man of about 40 with two children. About this time he introduced into his business, with a view to future partnership, a man B, aged about 25, with capital to invest. B was homosexual and knew it. A bond of friendship, then affection, grew between A and B which later led to overt homosexual practices. A's marriage disintegrated and his wife and family went to live abroad. After some five years of cohabitation A and B separated amicably, and they are still close friends.

A tells me that he had no suspicion that he was homosexually inclined until he met B. He had been reasonably happy. His marital obligations had been fulfilled adequately, but he had

realised that sexual intercourse interested him less than it seemed to interest most of his friends and he had supposed that he was "made that way". Since the break-up of his marriage A has led an exclusively homosexual life with no further interest in heterosexual activity. He is now chairman of a big company, a member of many committees, a prominent and respected figure in the community.

B, a man of considerable private means and strong religious convictions, is a bachelor. A practising homosexual who disapproves of promiscuity, he lives discreetly and unostentatiously with a friend of many years' standing in a community where he is respected by all. He takes no part in public life but some of his friends—like myself—know of his kindness and generosity to many people, mostly elderly and infirm men and women, a considerable number of whom he has supported for many years.

Case 3.—C is a senior captain in an airline. Now in his late 30s he is good-looking, virile, and self-confident, with a well-integrated emotionally stable personality. His sexual outlet in orgasms has always been high and still averages 5 to 6 per week. His sexual activity has always been predominantly, but not exclusively, homosexual. About six years ago, for a variety of motives (not all admirable) he married, and he now has a family. The marriage has been successful, and he is very fond of both his wife and the children. His work takes him away from home for about two weeks in every four. During these absences (but not while he is at home) he still leads a homosexual life. But he is worried. "What is going to happen when I stop flying and have to remain at home all the time? I don't think I could ever be exclusively heterosexual."

Cases 4 and 5.—D is a middle-aged doctor, a bachelor, successful and respected. He came from an emotionally secure home, had a happy childhood, has brothers and sisters, attended a boarding-school, and was never seduced by an older person. As a medical student he enjoyed the companionship of women and dancing. At the age of 21 he became engaged to a young woman whom he admired and of whom he was very fond. Intercourse took place often, but, though he was potent, he found it lacking in emotional and physical satisfaction. Finally the engagement was broken off because "the ritual of heterosexual intercourse" became increasingly distasteful to him and because he realised that the marriage, if it took place, would certainly end unhappily. He is sure that his fiancée never suspected the real reason for the break.

At the age of 30 he met E, aged 19, who was illegitimate, had had an unhappy childhood, and believed himself to be homosexual. They lived together for twelve years in mutual affection, respect, and happiness. D was able to bring educational and material advantages to E who now holds a responsible executive position in business. When E was 31 he fell in love with a girl whom he wished to marry. They have now been happily married for about eight years and have three children. D remains the closest of all the family friends, attends them all professionally, and is godfather to the eldest child. E says that he has never behaved homosexually since his marriage.

Case 6.—F, aged 25, is tall, well built, Scandinavian by birth. At the age of 15 he was warned by his mother that some of his friends were suspected of homosexuality and that he should be careful. "But I am homosexual," he replied. His mother told me of this incident. She sought advice from their (Scandinavian) family doctor who explained that her son might well change his mind later, but that, in the meanwhile, nothing would be achieved by argument or recrimination. He stressed that it was most important that the son should feel that he had the confidence, sympathy, and understanding of his parents in this matter. In due course the position became accepted by his family who decided that he had had no personal choice in his sexual orientation and that—for better or worse—he had the right to live his private life in his own way.

He is a cheerful extrovert, a keen and proficient ballroom dancer. He has many friends of both sexes but he tells me that he has never at any time in his life experienced any heterosexual desires. Genitalia are well developed but hair distribution is feminine, and he has little, if any, need to shave. He is not effeminate in voice or mannerisms, nor has he any transvestite tendencies. He is a hard and conscientious worker earning over £1500 p.a. in a business which gives him scope for his artistry and originality. He appears to be free from complexes about his anomaly, and says that he is content to be as he is. He is not promiscuous, does not frequent places where homosexuals are known to forgather, and hopes to find a permanent partner. In the meanwhile he has led a vigorous homosexual life in liaisons most of which have lasted several years.

Case 7.—G is a successful farmer, aged about 46. He has an open-air appearance, heavy build, sunburnt complexion, rather stolid manner. He served in the Navy during the war. It was not until he was about 35 that he became fully aware of his sexual orientation. He says that women have never attracted him sexually. He admits that several times during his naval service he was attracted by other men, but he was too frightened to make the first move and none of the others ever did. I do not know the circumstances under which he had his first overt homosexual experience, but he is now leading an active homosexual life—deliberately, I think, trying to make up for lost time. Like so many who discover their homosexual inclinations relatively late in life, he suffers from a guilt complex and from hypochondria.

Before I met him he had consulted a general practitioner who was believed to have had some psychiatric experience. When G explained that he was homosexual the doctor exclaimed "Good God! you don't look like one." The patient tells me that he spent most of the consultation answering, not asking questions ("Are there many of you about?"; "What do you really do?").

Although G has no heterosexual desires, he is active in a homosexual relationship.

Case 8.—H, aged about 35, works as a member of the aircrew of an international airline. He is a cheerful, uninhibited, stocky, rather tough type, full of bounce. His first wife divorced him when she discovered his homosexual tendencies. His second wife married him with full knowledge of these facts. She stipulated that, though he would be free to do as he wished with other men while away from home, she would not tolerate any affairs with other women. His sexual activity appears to be about equally divided between heterosexuality and homosexuality: in the former a sadistic tendency is apparent, whilst in the latter he prefers a passive role.

Case 9.—I, whom I have known for some eighteen years, is now about 38 and is a man of fine physique—6 ft. 4 in. in height. During the war he served as an A.B. in the Navy, and, though he had no lack of female admirers, his sexual activity was almost entirely homosexual. After the war he returned to work for the firm he had joined on leaving school, and for which he still works. He comes from a happy home. There has been no divorce, no alcoholism, and he says that he was never seduced by an older person.

Because he wanted a home and family he married shortly after the war. As he is a sensible level-headed person he chose a nice girl with whom, after some ten years of marriage, he is still happy. They have a family. He tells me that since the birth of their first child sexual intercourse has become of less and less importance to them. His wife "is wrapped up in the kids now and it does not worry me". He is still predominantly homosexual by inclination, but he lives a quiet domesticated life on a modest income in a home where he is happy; so, as he says, "I don't often get a chance to go off the rails." Nobody meeting him socially or in business would suspect for one moment homosexual tendencies.

Case 10.—J, now in his late 30s, says "I have always been homosexual—I knew that before I left school." During the

war he served in the Army. A successful businessman, he is a good mixer, an extrovert who rarely reads a book or remains by himself for any length of time. He has a large circle of friends, including many women (usually rather sophisticated types) with whom he is very popular. He shows no outward signs of homosexuality.

He has lately attempted heterosexual intercourse with a partner who was already aware of his tendencies. He said afterwards " It was awful, it brought me out in a cold sweat . . . the trouble is that a woman lacks the *only* thing I find sexually exciting . . . it was quite hopeless but luckily she understood."

Case 11.—K is 25 but looks younger. A self-taught but successful commercial artist, he is intelligent and a devout Roman Catholic. His father, an alcoholic, died some years ago. He lives in a student hostel but spends his weekends with his mother, stepfather, brothers, and sisters, with all of whom he gets on very well. Both at boarding-school and since he has had several emotionally intense homosexual relationships resulting in mutual masturbation. These affairs have caused him deep feelings of guilt and remorse as he considers any form of extramarital sexuality sinful. On the other hand, he has no wish to enter the priesthood. He often has bouts of depression, because he sees no solution to his problem. He has never had any heterosexual inclinations and is convinced that he is entirely homosexually orientated. He says " I can't help falling in love with other men." He says that marriage would be impossible for him; yet he knows that he will never be able to achieve complete sexual abstinence for long periods.

He has always wished to be a woman and has had to make deliberate efforts to suppress transvestite tendencies. In school plays he was usually chosen for female parts (which he enjoyed playing) but suffered many taunts for being effeminate. Now he is constantly on his guard, while making every effort to appear normal. In this he has been successful, for he shows no obvious signs of homosexuality in speech, manner, or dress. He is very interested in the recently publicised cases of change of sex which he wishes were possible for himself.

To his friends he seems to be a cheerful chap with a happy outlook, but he has admitted to me that he has several times seriously considered suicide as the only solution to his problem.

Cases 12 and 13.—L, aged 21, says that he has never had any heterosexual desires. Mesomorphic in physical type, he is virile in appearance and has larger than average genitalia; puberty was early. From childhood he has thought of himself as being female; many of his interests are feminine, and he says that, if he were offered the opportunity of becoming a " real woman ", he would accept without hesitation. At the age of about 10 he was friendly with a small girl of the same age. Their favourite game was to re-enact the film exploits of Tarzan and Jane, but he insisted upon being Jane whilst the small girl had to be Tarzan. He belonged to an average happy family, with normal brothers and sisters; no divorce, or evidence of an emotionally disturbed background. His work has now taken him away from his home town.

At the age of 13 he was introduced to mutual masturbation by a middle-aged man. I have discussed this incident with him at some length and he is emphatic that the experience did not determine his sexual orientation of which, he says, he was already aware. He admits that he probably encouraged the incident, says he was not in the least frightened or upset by it, and anyway knew what to expect. " I still write to the old boy —well, a card at Christmas anyway." From the age of about 16 he has had many homosexual partners of his own age, but most of these affairs have been unsatisfactory. He says that he does not want to be promiscuous and that " sex without affection is wrong ".

A little over a year ago he formed an intense emotional attachment to M, an older man (38) with whom he works and who—though homosexual—at first showed little interest in him. M does not resemble at all the conventional picture of a homosexual—quiet, masculine manner, well built, a pipe-smoking beer-drinking type. These two have now shared a flat for nearly a year, with L doing all the housekeeping. M has undoubtedly become very fond of his young friend, whilst L idolises his partner. L is a conscientious and hard worker who is very popular with the rest of the staff, both men and women, and he has been promoted twice with rises in salary during the past year.

Case 14.—I first met N, now 45, about fifteen years ago when he was a sergeant in the army—an ordinary, friendly, not very intelligent, but very likeable person—whom I had reason to believe was completely homosexual in his habits, though there were no outward signs. After the war he joined a friend (not homosexual, but tolerant in outlook) in a retail business which is now prospering.

I have known for some years that, though he is still a practising homosexual, he wished to get married. The reasons were, I believe, that he was lonely and wanted companionship, that he wanted marriage as a camouflage for his reputation, and because he believed that sooner or later the alternative would be a police prosecution. Three years ago he married a woman he has known for many years, aged about 40, a comfortable, homely, placid person. There is no doubt that he is trying to be a good husband, but it is equally clear that he is no less homosexually inclined than he was. He still occasionally behaves homosexually if temptation and suitable opportunity offer. Afterwards he is very remorseful. When I asked how the sexual side of his marriage was going, he replied, rather guardedly, " Oh, all right," then changed the subject. I hear that his wife is shortly going on a long visit to her family. I hope that this is not a prelude to a breakup of the marriage.

Case 15.—O, now 48, a man of independent means, widely travelled, had always been predominantly, but not exclusively, homosexual in his habits. In his late thirties he met a rather unusual, attractive, intelligent young actress, cosmopolitan in outlook like himself. They became very fond of each other and finally married. For five years all went well; they shared many interests in common, travelled extensively, and seemed to be happy together. Then the break came—I do not know the details. They still correspond in a friendly way, but live in different countries. There were no children and she has not remarried.

He has now lived with a man of 28 for several years. Neither O nor his friend is promiscuous and they do not mix in any homosexual coterie. O said to me recently " This is the only way I can live. The other was an unnatural existence for me and I could not keep it up any longer."

Case 16.—P is a bachelor now in his mid-80s. He comes from a socially prominent and prosperous family. During his student days he travelled extensively, studying languages. He was tall, a keen athlete, and, he says, a good-looking young man. One of his tutors, several of his student friends, and some acquaintances on his travels made homosexual advances; but these shocked him. He had a distinguished Service career in the first world war.

As he became older he realised that he was predominantly homosexual in orientation, but his family background and training had taught him that this was reprehensible; so he did not allow any homosexual behaviour to occur. He tells me that he never discussed his inclinations with any person until about five years ago when he did so with me. His knowledge of the subject up to that time was derived from reading Greek and other classical writers. It appears that not until after his 50th year did he have his first experience of sexual activity with another person.

He is now obsessed by the thought of his " wasted youth ". It distresses him to find that it is the physical beauty of the youth of both sexes—but particularly young males—which attracts him. He admits that mutual masturbation with young men in the 16–20 age-group has occurred often during the last thirty years, but no sexual acts with women or older men. Since a prostatectomy a few years ago these incidents have ceased or, at least, become less common. He says that if he had had some sexual fulfilment during his youth and maturity he would now be content to " grow old gracefully ".

In his community he is liked and respected and his personal problem is unsuspected by his friends and neighbours.

These case-histories have been selected from a much larger number to illustrate different types of male homosexual. All are known to me personally, none shows any outward signs of homosexuality (except possibly no. 6), only one (case 16) is sexually interested in adolescents; only one has sought medical advice. None of them has ever been on a police charge for a homosexual offence. None of them knows of any reason why they are homosexually orientated, and all agree that seduction in childhood by older persons was not the cause. I have attended most of them professionally, but none of them consulted me because of homosexuality.

Discussion

Cause

It is my considered opinion that the cause of homosexuality is still unknown. One day the heterosexual man finds he has heterosexual desires: one day the homosexual man, usually to his embarrassment and distress, finds that he has homosexual desires. Neither has had the slightest choice in his sexual orientation. Likewise, one day the ambisexual discovers that he reacts erotically to both sexes.

Heredity seems to play no part, nor does genetic abnormality or endocrine disturbance seem to be responsible. The involved, and often conflicting, ætiological explanations advanced by psychiatrists I find unconvincing. Their theories may appear reasonable when confronted, in the consulting-room, by a neurotic, hysterical, immature or otherwise emotionally disturbed homosexual patient, but most homosexual men are well adjusted and, apart from their sexual anomaly, no different from their fellows. Can these psychiatric theories, based on a disturbed parent-child emotional relationship in a highly developed Western civilised society, explain homosexuality among primitive, uncivilised, often polygamous tribes?

Criteria of Treatment

The words "cure" and "treatment" are used too freely by doctors, judges, magistrates, and lawyers, with little regard to the facts. For the homosexual cure can only mean the reorientation of his desires into heterosexual channels. Chastity, adopted for moral, religious, or legal reasons or enforced by chemical castration, is not a cure for homosexuality. As far as I am aware homosexually deviated instincts have never been permanently reorientated into heterosexual channels. Claims have been made but none have ever been submitted to the criteria for other medical claims—namely, independent scrutiny and adequate lapse of time to prove permanence. To accept marriage, or an intention to marry, as a criterion of cure is unrealistic.

Another factor often overlooked when cures are claimed is that the homosexual who goes to a psychiatrist for treatment is usually already in trouble with himself (feelings of guilt, depression, or inferiority), with his family (scandal or disgrace), or with the police. He is desperately anxious to be cured and only too glad to accept the psychiatrist's assurances. Disillusionment comes later.

Incidence

There are as yet no reliable figures for the incidence of homosexuality in Britain. Kinsey's figures,[1] based on his nine-year survey in the United States, are probably equally applicable in Britain but are generally scorned, not because any evidence to refute them has been produced during the past ten years, but because to most people they are "unpalatable".

The homosexual in Britain is not only a potential criminal but usually also an undetected criminal. To allow his anomaly to become known will usually deprive him of most of his friends and perhaps of his livelihood. Is it surprising, therefore, that most of these men take adequate precautions to camouflage their anomaly? Is it surprising that the general public persistently and grossly underestimate the number of homosexuals in this country?

My experience as a homosexual over the past thirty years has convinced me that at least 10% of adult men fall into the Kinsey ratings 4, 5, and 6. In Britain this means that between $1^1/_2$ and 2 million men are predominantly homosexual. Investigations I have made in several European and non-European countries leads me to believe that the incidence varies little, if at all, from country to country.

Behaviour

In discussions of homosexuality the physical aspects tend to be overemphasised while the emotional aspects are overlooked. Yet these may be as intense as those experienced by heterosexuals. Many homosexual friendships, like many heterosexual friendships, do not include physical acts. The homosexual liaison—unlike marriage—is unsupported by legal, social, economic, or family considerations tending to encourage permanency. I do not believe that homosexuals are inherently more promiscuous than heterosexuals would be if they had to live under similar conditions of loneliness and sexual insecurity.

Lesbianism, fornication, adultery, rape, even murder can usually be discussed calmly and objectively, but male homosexuality rarely. It seems likely that the illogical and disproportionate emotional reaction produced in some people—usually men, not women—by this subject is caused by unresolved conflicts. It is widely believed among homosexuals that exaggerated revulsion is an indication of latent homosexual tendencies.

Homosexual problems are often the cause of alcoholism and suicide, though the basic reason for these tragedies is rarely disclosed and usually unsuspected.

I make no attempt to defend the immorality disclosed in many of the case-histories, beyond suggesting that it should be judged alongside heterosexual immorality.

Conclusions

The case-histories I have described support the following views:

Some men are wholly homosexual and incapable of heterosexual relationships (cases 2, 6, 7, 10, 11, 12, 13).

The main sexual pattern is laid down in the early years of life (cases 6, 9, 10, 11, 12).

Neither heterosexual nor homosexual activity, even when continued over a period of many years, seems to alter the underlying basic sexual orientation (cases 1, 3, 5, 8, 9, 14, 15).

Homosexuals are reluctant to seek medical advice because:

They believe that most family doctors share the ignorance and the emotional prejudice of the layman on this subject.

Most of them know that medical treatment cannot make them heterosexual.

People, including doctors, find it easy to preach lifelong chastity for others when they do not have to practise it themselves.

1. Kinsey, A. C., Pomeroy, W. B., Martin, C. E. Sexual Behaviour of the Human Male. Philadelphia and London, 1948.

The Widdicombe File

LVII.—DE MORTUIS

DEAR HARRY,

Don't you think that you and I ought to do a spot of rethinking about our public mortuaries and postmortem rooms? No-one else seems to want to do it. In fact I dare say you have noticed how most people keep their eyes tight shut and pretend that such places do not exist. I often think that there must be a very thin line between fiction and reality for acceptance. Sweeny Todd is rip-roaring fun, the latest murder headlines are fascinating, the death-on-the-roads posters are queasy, but the real thing is more than the laity can face. Maybe that is why we are getting into such difficulties with our mortuaries. But first let me tell you how we are laid on on our side of the Moor.

This generation has lost sight of the fundamental distinction between a mortuary and a postmortem room. Once upon a time our forebears were quite clear about it. They had to cope with body-snatching. That was why the law of England stepped in to forbid the holding of post-mortem examinations in public mortuaries. But Burke and Hare and their disciples faded in human memory, and the law seems to have lapsed since then. The mortuaries turned into a free-for-all down our way, with the general practitioners doing as they pleased. After all, it was out of the question to take a horse-drawn hearse some twenty-five miles each way for the hospital pathologist to do what could be done just as well in the shed behind the police-station. Maybe the place was not very good, but it was essentially a village rite, so no-one was too critical.

But fashions change and so do coroners. The time came for the general-practitioner morbid anatomists to be elbowed out. A pathologist reigned over the Moor. He did not think much of our villages. The roads were bumpy, the bacon too fat, the beer was warm, and the public mortuaries were well-nigh impossible for any self-respecting and respected consultant pathologist even to roll up his sleeves. He moaned and he grumbled and swore at old George. All most unreasonable. How could we heat the old stone shed while he did his fancy post-mortems? Or lend him more than two oil lamps? Or carry another water bucket from the well on the green? And George slaughtered pigs every Thursday, so surely he was competent enough to help this new high and mighty lordship? Anyway, George had always given satisfaction to old Doctor Elijah, the one that used to wear the frock coat.

You can guess what happened next. The pathologist demanded that his clientele should be taken to him at the hospital. That left us nearly back where we started. The occasional eccentric reactionary general practitioners continued to pursue ultimate truth in the traditional spot, but even they started to fret for more gadgets. The local councils took one look at their responsibilities and then firmly shut their eyes. Economy is easier if needs are ignored.

So there they stand today, the village morgues of England. Silently used half a dozen times a year as an improvised left-luggage office for a passing corpse, smuggled in and out with our ashamed apologies. Less silently when a bereaved relative is shocked to protest at our decrepit service. Explosively when the coroner or the pathologist have to go there in their line of duty. Most of our public mortuaries are historical relics.

There is the one at Torricombe Magna behind the pinfold. The whitewash inside has perished, the spiders' webs remain. A stained rubber apron and a hosepipe hang by the door. An erstwhile pathologist's rusty ironmongery is only too obviously on view. The outside of the building is nearly covered with brambles and moss, like some fantastic ballet scene from *The Sleeping Princess*.

Then there is the one at Lindworthy, next to the piggery, with all the pig manure piled high in the sun against the south wall. Fitted out like a butchery, but none too clean. With some scraps of clothing from last month's car crash on Lindworthy Hill.

And so the list goes on . . .

The point is, my dear Harry, that these country places are still in use. A confused use maybe, neither properly mortuaries nor postmortem rooms: neither properly administered nor officially abandoned. Just indecent sordid relics of our past history. But the troubles do not end with their decaying structure and outmoded styles. Administrative amnesia can produce the most curious results. One of our public mortuaries on this side of the Moor deteriorated to the stage when no one would accept responsibility for it, and the odd-job caretaker's nominal retainer fee had sunk to an untraceable entry in the account books. Another one was comfortingly believed for some twenty years to belong to the police authority, until the auditors remarked upon such an impossibility. The west end of the one at Clam Bay seems to have been converted into a public convenience without anybody missing it.

At Lindworthy, as I told you, there is a steady demand on the mortuary for people who come to grief on the steep section of the Hill by that telegraph pole on the corner. The police have established a virtual monopoly there. They put bodies into the mortuary, and they take them out again, without ever telling the caretaker. And then people howl with indignation when the place is found dirty when next required. The poor old caretaker is supposed to work some sort of a crystal ball to know what goes on.

I think you will agree that it is rather irritating to have unheralded corpses dumped into your mortuary, and particularly disconcerting to meet one unexpectedly. Even more disturbing is the thought that they can disappear from the slab without notice. It takes us full circle back to Burke and Hare. Mark you, Lindworthy public mortuary is more obliging than most: the key is kept hanging on the door post. It shows a touching faith against malice, morbid curiosity, practical jokers, and other contemporary phenomena. Anyway, easy come and easy go is Lindworthy's philosophy of life and death. They keep no records of those they accommodate, and ask for nothing in return: not even to be told when the house is full.

At Poolcombe Bridge there is a different problem. Whose job should it be to clean up the corpse, perform what are euphemistically called the last offices, and lay out the body for bereaved relatives to identify? The police used to do it: they are a long-suffering profession. But the Chief Constable then decided that it was no part of their duty. So the mortuary cleaner was asked to do it. He refused pointblank. After all, he was the steamroller driver, and was only supposed to look in at the mortuary on the second Tuesday in the month to see that there were not too many cobwebs. He wouldn't go near the place at any price when there was One of Them inside.

Deadlocks like that never last long. Up came the local St. John Ambulance Brigade and volunteered for the job. Very noble of them; but, my dear Harry, what do you

think of the general principle of permitting unpaid unofficial volunteers to come into a public mortuary for that purpose? Don't you think it is fraught with all sorts of risks? The proper answer no doubt is to sack the steamroller driver and appoint someone else who will do all the necessary cleaning up and laying out. The snag is that no-one else in Poolcombe Bridge will take it on.

Such people are very hard to find. Moreover there is the question of compatibility with their other part-time jobs. I should hate to think of anyone in the food trade running the mortuary as a sideline. At Clotworthy village they employ the local undertaker, a most suitable dual role in my opinion, although his critics say that he is being shown undue favouritism over his trade competitors. It just shows that you can't please everyone.

The best that can be said for these countryside public mortuaries is that some of them still serve some sort of a useful function for the temporary storage of uncoffined bodies, including a preliminary clean-up.

May not these mortuaries be as obsolete as our mounting blocks, windmills, and public wells? In these days of motor transport would it not be much more sensible to reorganise all our public mortuary services upon the hospitals which serve the area? Most of the postmortem examination cases go there already, for the convenience of the pathologist and the coroner. The few extra are not likely to overtax the hospitals, and a small fee from the local authority would not be inequitable. The hospitals have better mortuary attendants, the advantages of refrigerator accommodation, and a much more seemly atmosphere for the bereaved. I suppose that undertakers' funeral parlours might be an alternative, but there are few signs that our British firms are keen to keep even coffined corpses on their own premises. No, I think that we could very well base all our mortuary and postmortem services on the hospitals. Could you cope at your end?

It may not be a very cheerful topic to write about; but don't you think that you and I, as a consultant pathologist and a medical officer of health, are the only people likely to give a lead to the rest of the community, by dragging these dusty relics out into the light and seeing what on earth we can do to think up something better?

Yours sincerely,
TOM COBBLEIGH.

Parliament

QUESTION TIME

War-damaged Hospitals

ON Dec. 1, in the House of Lords, Lord STONHAM asked H.M. Government whether, in cases where the hospital capacity of a district remained inadequate, they would authorise the payment out of war-damage account of the cost of repair or replacement of war-damaged hospital buildings in that district.—Lord ST. OSWALD replied: Under the National Health Service Act, 1946, any payments from war-damage account must be appropriated in aid of the National Health Service vote—that is, set off against expenditure on that vote. This means that any such payment made would be compensated by a reduction in the amount at that time available to the service. This being so, the adoption of the noble Lord's proposal would not particularly help the regional hospital boards or increase hospital building.

Until 1952, regional boards were allowed to claim war-damage payments, but as these were appropriated in aid to the N.H.S. vote, and as the amount of building was limited by a ceiling on investment, it led to no increase in building. The procedure was therefore abandoned as wasteful of time and effort. The Government's view is that the proper course is to rely on the regional boards to decide the spending of their own funds, and not to give any special priority to the repair of war damage.

Lord STONHAM: Is the noble Lord aware that his reply confirms that nothing whatever is paid on war-damage account for the repair of war-damaged hospitals, and that means that in the metropolitan areas a great disability is inflicted on many of our older hospitals which are in the worst condition? Would he look at the point that the capital programme for hospitals has been fixed for the next three years, which means that, unless there is a change in the present procedure, no help can be given to hospitals which are badly war-damaged—and this does not apply to any other kind of building—and which have no help even to pull down buildings that are dangerous?—Lord ST. OSWALD: I think the noble Lord was referring specifically to, for instance, St. Matthew's Hospital, which forms part of the central group of which he is chairman. For that reason, I have looked into the condition of that hospital, and I find that one block was severely damaged during the war and made weatherproof some years ago. The interior has not been reconditioned, because the need for additional beds has never been demonstrated to the satisfaction of the regional board which is responsible for the planning of hospital services in that region. The hospital has 320 chronic sick and geriatric beds to serve a population of 145,000—that is, a ratio of 2·2 beds per 1000, which is nearly twice the national average. The yardstick of need is not the national average but the need in a given locality. I have tried to study the noble Lord's own particular area, and I cannot find that there is a case where the need for expansion is held down artificially by reference to the national need.

Lord STONHAM: While I am grateful to the noble Lord for the detail into which he has gone, I was not referring to a particular hospital—indeed, I should have thought it would have been improper for me to do so. But can the noble Lord look at this matter with regard to the national position? St. Thomas's Hospital, we are informed, is to be rebuilt at a cost of £7 million, which is largely justified—and I do not dispute it—on the ground of war damage. That £7 million would resolve almost all the war-damage difficulties of almost all the hospitals throughout the country. Can the noble Lord not consider that and again have a look at the question of war damage at ordinary hospitals?—Lord ST. OSWALD: My Lords, I am sure I should be right in saying that St. Thomas's Hospital is being rebuilt on the grounds of need and not simply on the grounds of war damage.

Intercepted Telephone Conversations

On Dec. 3 Mr. GORDON WALKER asked why in view of the Government's acceptance of the report of the Committee of Privy Councillors on the interception of communications (1957 Cmd no. 283) there was a disclosure on Nov. 24 to the Disciplinary Committee of the General Medical Council of a record of an interrupted telephone conversation.—Mr. R. A. BUTLER, the Home Secretary, replied that he understood that the police listened to the conversation on a private extension of a telephone with the consent of the subscriber in the course of criminal investigations made at the request of the deputy-coroner. The solicitor to the G.M.C. learned of the existence of a record of the conversation from the subscriber concerned and subpœnaed the police to produce it. In answer to the subpœna, there was no alternative but to produce the document unless privilege had been claimed and granted. Mr. Butler had considered this very carefully on the advice of the Law Officers and came to the conclusion, on balance, that public interest was not to claim privilege on this occasion. He added that in his view this was a borderline case of the claiming of privilege and he was ready to discuss the application of future cases and the question of privilege relating to them on the basis of that example.

Mr. W. GRIFFITHS pointed out that this was a serious matter, because there was before the House a Bill designed to set up disciplinary machinery for a large number of medical auxiliaries, who would be exposed to the same conditions as was the doctor before the General Medical Council, unless the Government did something to prevent this sort of thing from happening again. Mr. BUTLER said that the disciplinary organs which might be set up under the Professions Supplementary to Medicine Bill, was a matter for the House. It might well be that the offer he had just made—that the bounds of privilege should be further examined—was one which he should take up at the request of the House with the Law Officers and the Lord Chancellor.

Royal Commission on Remuneration

The Royal Commission hope to present their report in February.

Public Health

Food-handling

80% of all outbreaks of food-poisoning in England and Wales in 1958 were due to meat, and 65% to some form of "made-up" meat.[1] These figures have not altered much in the last five years, and yet we are still ignorant of the source of most of these infections. A few diseased beasts reach the market and a few infected sausages are detected in the shops, but the majority of outbreaks cannot be traced any further backward than the dish on which the food is served. Since the outbreaks are due both to salmonella and to various other organisms which produce enterotoxins, it is proper that remedial measures should be applied at every stage of meat production between the pasture and the table. Some of these will be, no doubt, a waste of time; but we must hope that the sum of them will reduce the rather scandalous total of preventable disease. We cannot blame the farmer if he limits his interest to those diseases which reduce his profits: even with skilful veterinary assistance he is unlikely to detect the chronic carrier of *Salmonella dublin*. Nowadays meat inspection is a frail barrier, and it is no secret that, owing to shortage of staff, some of our home-killed meat is not inspected at all. A slaughter-house is always likely to be a dirty place; but there is a lot of difference between the best and the worst, and the same is true of the butcher's shop. Many branches of the meat trade attract staff whose strength and dexterity are more noticeable than their refinement and education. Two codes of practice, directed to the retail trade and the transport of meat,[2 3] which have been issued by the Ministries of Health and of Agriculture, Fisheries, and Food, are welcome evidence that the need for higher standards is recognised.

The value of many of the suggestions made in these codes is not easy to assess because there is no evidence that they have any direct bearing on food-poisoning.

It is desirable that rooms should have smooth walls and impervious floors; but is food from such rooms less likely to be a vehicle of food-poisoning than food from less sightly places? No-one knows. It is a pity that these general directions for improvement are given the same space and prominence as those which experience shows have some connection with disease. Employees with mild diarrhœa or with infected cuts on their hands are a real danger which receives adequate mention, but protection against this risk is left as a pious hope. A well-documented outbreak of salmonella infection was partly due to using the same knife for raw meat and corned beef.[4] The directions for cleaning equipment (para. 44) would not have prevented this catastrophe. It is suggested that wiping-cloths should be sterilised by boiling (which is admirable) or by a "suitable chemical sterilisant". Apart from the unpleasant, needless, and inaccurate neologism this phrase is totally unsatisfactory: what the butcher wants is precise directions on a suitable disinfectant and the strength at which it should be used. Other examples of imprecision can be found on many pages. "Care should be taken that brine is maintained in a clean condition". No fluid in which meat is soaked is likely to be "clean" by any standards, and brine is not at its best until it has been used several times: it probably needs to build up its own microflora to produce tasty bacon. The direction is in fact meaningless.

The booklet on the handling of meat in transit is far better and includes some good diagrams of the tackle required. But the editors of both could take some hints from a little pamphlet, *Clean Food Handling*, published by the corporation of the City of London. There is nothing new in it, but for practical common sense it is the best of its kind that we have seen.

The political atmosphere today is unfavourable to compulsion, and, where there is reasonable doubt whether orders can be enforced, codes of practice tend to replace statutory instruments. Against this there is the obvious argument that the best already do as the code suggests and the worst will throw it away unread. Most retailers, however, fall somewhere between these two extremes, and when pressure from customers is reinforced by official arguments some good is likely to result. Freed from fears of retaliation the housewife today is prepared to argue, to complain, and to remove her custom, and it would help her if she were to know what the Ministries have advised in these publications. To the health inspector a code of practice is certainly more trouble than a set of rules but possibly in the end more profitable. He cannot compel but he can advise and demonstrate, and as a friendly propagandist is likely to do more good than as an arm of the law. He was not a popular figure in the farming world when he was responsible for the production of clean milk, and that he often did not know how to milk a cow lowered his reputation even further. We hope that these codes of practice will persuade the meat trade that the health inspector is not intent upon prosecution and punishment but very eager to save us, one and all, from preventable ill health.

1. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 169.
2. Hygiene in the Retail Meat Trade. Food Hygiene Codes of Practice no. 1. H.M. Stationery Office, 1959.
3. The Hygienic Transport and Handling of Meat. Food Hygiene Codes of Practice no. 2. H.M. Stationery Office, 1959.
4. Camps, F. E. *Mon. Bull. Minist. Hlth Lab. Serv.* 1947, **6**, 89.

Infectious Diseases in England and Wales

Disease	Week ended November			
	7	14	21	28*
Diphtheria	3	8	21	13
Dysentery	443	538	572	657
Encephalitis:				
Infective	2	5	2	4
Postinfectious	..	..	3	1
Food-poisoning	177	147	206	201
Measles, excluding rubella	1196	1071	984	1174
Meningococcal infection	14	17	10	20
Ophthalmia neonatorum	18	19	28	15
Paratyphoid fever	9	4	..	1
Pneumonia, primary or influenzal	177	180	267	284
Poliomyelitis:				
Paralytic	12	21	11	11
Non-paralytic	2	3	5	5
Puerperal pyrexia	200	223	186	172
Scarlet fever	1025	1062	1382	1463
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	430	370	446	407
Meninges and C.N.S.	3	2	4	8
Other	47	53	46	39
Typhoid fever	3	8	3	3
Whooping-cough	568	641	714	696

* Not including late returns.

In England Now

A Running Commentary by Peripatetic Correspondents

AMONG the most delectable things in our Edwardian childhood were aunts. This thought surfaced in my mind yesterday while I was reading a discussion on the health-promoting or "salutiferous" community. In all the talk of the mother and the young child, the family, the old person, and the rest there wasn't one mention of aunts. (I mean unmarried aunts, of course. Married aunts are not the same thing at all.) Are aunts obsolete, like the milkman's horse? If so, we are all the poorer. Let our psychiatrists look to this failing resource in our modern age. All the emphasis on marriage and sexuality and the mother-child relationship may well be undermining the confidence of girls in their potential role of aunts. Let us have some more positive thinking. Let us give some support to these neglected members of the community. Perhaps a series of pamphlets? *How to be the Perfect Aunt, The Challenge of Aunthood, Preparing for Aunthood, Whither Aunts?*, or *The Role of the Aunt in Our Changing Society*.

Dear, delightful Aunts, past and present, if anyone was salutiferous, it was you.

* * *

I, too, read the article on dog bites which you discussed in an annotation last week, but I read it rather late at night and somehow misinterpreted the title as meaning bites suffered by dogs. In Pittsburgh, I gathered, questionnaires had been sent to "practising veterinarians, personnel working in animal hospitals, members of the Animal Rescue League and the police"—all people, one would think, to whom dogs were likely to complain if bitten. A vast amount of information had been collected. Thus 79% of dog bites occur between noon and midnight, with a seasonal peke—sorry, peak—in the summer months. Personally I seldom bite my dog after midnight, but it was certainly "difficult to explain why only 15% of the bites occurred from 6 to 11.59 A.M." Working breeds as a group had 90 reported bites against only 48 expected ($P = < 0{\cdot}001$). Who has not bitten the St. Bernard that failed to bring the brandy? But when the occupations of the victims were examined it became clear that the darling doggie-woggies were the biters, not the bitten. "If newspaper boys and mailmen were included among persons going to the dog owner's home in the line of work"—and why not?—"then 13 per cent of all victims were in this occupational category." *Eheu fugaces, Postifer, Postifer, Mordentur bracae. . . .* But what made my English blood fairly boil (100°C) was a recommendation that dog owners should "restrain or dispose of dogs which consistently bite people". Will nothing stop these callous scientists? À la lanterne! Workers of the (canine) World, Unite! "Dispose of" indeed—accept their resignation, perhaps.

A Doberman Pinscher of Pittsburgh, Pa.
Told his sorrowful master he could not stay.
Since Parrish, Brobst, Mock, and Clack, Frank B.
Had published his highly significant P.

Anyhow, I am told on good authority that Doberman Pinschers, being German, always say *bitte* when biting a lady.

* * *

An Englishman's home, though small, is his castle; and in this castle the keep and final stronghold is the smallest room of all. Yet in other, less fortunate, countries this security cannot be taken for granted. We read, for example, that on Feb. 5, 1958, a deputy of the French National Assembly exploded a plastic bomb in one of the lavatories of that building. The *Guardian* [1] informs us that "The Assembly was not sitting and no-one was hurt". Even so it is hard to imagine an act of anarchy more calculated to undermine the foundations of society and cast doubt on the seat of Government. It is somehow reassuring to know that in France the penalty for damaging buildings with explosive can be death; evidently our neighbours across the Channel are ready, at a pinch, to award an adequate sentence for this fundamental crime.

* * *

1. *Guardian*, Nov. 30, 1959, p. 1.

The tribulations of your peripatetic non-combatant Chinese boxer call to mind my own achievements from the other end of the adiposity spectrum. My truncated pugilistic career started, not at school as usual, but in the first full flush of university life, when one is so easily persuaded to partake to the full of the many opportunities offered. I spent long hours in the gym wearing little shorts and being introduced to the hook (left and right), the uppercut, and other mysteries by a minute and incredibly agile Nigerian law student. After a week or two I found myself, to my amazement, entered for the inter-faculty championships. Thanks to the rule that gives a point for every competitor entered, the medical faculty had won the day before the contest began. Even had every bout gone devastatingly against us we should still have emerged clear victors. The organisers indeed found difficulty in summoning enough candidates from among the engineers, theologians, scientists, and so on to give all of us bloodthirsty medicals a fight each, particularly me at 15 stone or more and amounting to a sort of heavier-weight. Loth to disappoint me, they went to great trouble to find an opponent and at length matched me from the audience with a fellow-medical who had taken a good five pints since tea and was in a cooperative mood. This amounted, of course, to an exhibition bout, and it certainly was. My doughty opponent gave away some 10 years and 5 stone and discovered after 15 exhausting seconds milling around that his boxing was further away than he thought. He subsided to the floor for a count of 9 before rising and falling at 2-second intervals for further counts of 9 until the end of the fight—not because I hit him but to get his breath back. However, my best friends told me that despite this victory I was not really cut out for boxing. So I retired at the peak of my career with my cortex intact. Or so I like to think; but perhaps I had better ask my best friends about that too.

* * *

A VISION OF ICONOCLASTES

I hope that I may live to see
Rich fruits in plenty on each tree—
A brace of cars to every home—
Each house a private aerodrome—
An ice-box and a wash-machine—
Computer-driven haute cuisine—
Let technologic wealth increase
And flourish, in the name of peace:
But Prince, remember, on your Western throne
Man lives not by consumer goods alone.

Others may force the scientific pace—
Escape from boredom into outer space—
Create, with art and subtle intellect,
The Machiavellian lie direct—
Inflate themselves with crude self-praise
Abusing all who favour different ways—
And, if they wish it, they may smile
At *Truth* and weep with *Crocodile*:
But Prince, remember, on your Eastern throne,
Man dwindles, self-sufficient and alone.

We walk a slender rope indeed
And balance various kinds of need;
There is no shame in wealth, no harm
In pride, so long as hearts are warm;
A lie may be a parable, a paradox a lie—
For men have need of doctrines to deny
And yet, denying them, still give their share
Since only exercise keeps Freedom in repair:
So, Princes all, remember on your thrones
That *men are more than sticks and stones.*

L'ENVOI

Lo! East is East and West is West
And one man's pants are another man's vest—
So, Prince, continue to advance,
Intolerant of intolerance.

Letters to the Editor

DECUBITUS BLEEDING

Thank God my Afflictions are such
That I cannot lie down on my Bed,
And if I but take to my Couch
I incessantly Vomit and Bleed.
from An Eighteenth-Century Calvinist Hymn
by JOHN BETJEMAN.

SIR,—The proper management of hæmatemesis is a topic that regularly provokes controversy. Over the past three decades diet, transfusion, and early surgery have been, in turn, debatable points, and in these respects the present standard treatment of hæmatemesis differs vastly from that practised thirty years ago. Yet about one aspect there seems to have been universal if tacit agreement: the patient who has vomited blood is nursed lying flat with no more than one pillow. A well-known textbook [1] contains the following instructions: "The room is kept quiet and semi-darkened, the patient's head is kept low and the foot of the bed may be raised." In the wards of a busy general hospital, compliance with the first two of these precepts may be difficult but the third, to keep the patient lying flat, is a routine known to every nurse.

In the cases described below the traditional head-low position seemed to have been harmful and to have encouraged further bleeding.

CASE 1.—A primigravida, aged 30, twelve weeks pregnant, vomited about a pint of blood on Nov. 17, 1953, and again on Nov. 19 when she was admitted to hospital. For many years she had suffered from heartburn and, for the past three months, from morning sickness and occasional epigastric pain. On arrival at hospital her condition was reasonably good: pulse 108, blood-pressure 130/80 mm. Hg, hæmoglobin 69%. There was no abdominal tenderness. She was nursed lying flat, with one pillow.

On Nov. 20, after a day of much epigastric and retrosternal discomfort and much vomiting, there was a further hæmatemesis. The hæmoglobin had fallen to 54%. Two pints of blood was given slowly by drip transfusion and on the following day, after another hæmatemesis, a further tw pints was transfused. On Nov. 22 the patient was still restless and distressed, and after transfusion of a further five pints the hæmoglobin was only 62%. On Nov. 23 she had her fifth hæmatemesis. The blood-pressure had now fallen to 100/40.

At this stage, during a reassessment of the case, the long history of heartburn, previously overlooked, took on a new significance, suggesting that the bleeding might arise from the œsophagus. Instructions were therefore given to sit the patient up in bed against a back-rest.

Within an hour or so she was free from all distress, and after this change in position there was no further vomiting. She was well enough to return home on Dec. 5, the stools being consistently free of occult blood. On Dec. 10. a barium meal showed some deformity but no tenderness of the duodenal cap. No hiatus hernia or gastro-œsophageal reflux could be demonstrated. On May 25 she was normally delivered of a healthy female infant.

CASE 2.—A man of 25 fainted in the cinema on the evening of Dec. 9, 1958, and shortly afterwards vomited about half a pint of blood. He came into hospital the same night. There was a history of intermittent heartburn and of epigastric discomfort for three years. The symptoms were unrelated to food and occurred chiefly in bed at night. The patient, an athletic and well-nourished young man, was pale and sweating: pulse 68, blood-pressure 100/60, hæmoglobin 85%.

He was nursed lying flat and, because of his shocked condition and his low blood-pressure, the foot of the bed was raised.

Sixteen hours later the patient vomited a pint of fresh blood. The blood-pressure had not risen above its original level and the hæmoglobin was 65%. A drip transfusion was begun and over the next twenty-eight hours seven pints of blood were given. On Dec. 10 there was a further hæmatemesis of two pints. The blood-pressure had fallen to 80/40. At this point, despite the patient's poor condition, the experience of case 1 encouraged me to give instructions that the blocks be removed from the foot of the bed and the patient be nursed reclining against a back-rest.

The patient's discomfort was relieved almost immediately and he never vomited nor bled thereafter. On Dec. 12 the blood-pressure was 125/80. On Jan. 1 he left hospital. A barium meal on Jan. 9 showed no abnormality of stomach or duodenum, and no hiatus hernia nor gastro-œsophageal reflux could be shown.

In each of these cases, the turning-point in a rapidly worsening condition followed so soon upon a simple change of posture, that all observers were convinced that it was indeed this change of posture that had brought about the improvement. Clearly no generalisations may safely be drawn, but the fallacies of post hoc propter hoc reasoning are minimised by: (1) The almost simultaneous onset of recovery with a change in treatment; (2) the rate of recovery thereafter; (3) the objective nature of the improvement (the first patient had required nine pints and the second eleven pints of blood before bleeding stopped).

As to the cause of the bleeding, both cases must fall into the category of hæmatemesis of doubtful origin. While the history of heartburn suggested œsophagitis, X-ray examination gave no support to this diagnosis and in the first case was indeed suggestive of duodenal ulceration. Hiatus hernia is, however, often difficult to demonstrate and is, in its early stages, usually reversible. It often complicates pregnancy and is frequently found in association with duodenal ulcer.

Wolverhampton. J. V. S. A. DAVIES.

1. Dunlop, D. M., Davidson, L. S., McNee, J. W. Textbook of Medical Treatment. Edinburgh, 1949.

TREATMENT OF BLEEDING PEPTIC ULCER

SIR,—I read with great interest the two articles on hæmatemesis in last week's issue. The management of bleeding peptic ulcer needs real cooperation between physicians and surgeons, and when this is achieved a general hospital is able to reduce the overall mortality to within the range of 4–7%. A policy of selected surgery is needed, operating particularly on patients with known chronic ulcers and recurrent bleeding after admission. The extent of selection varies, and some prefer to operate on any patient with known chronic ulcer on admission without waiting for further bleeding (which happens in 25–30% of admissions). The effect of any change in policy can always be assessed by the revealing overall mortality figure. The particularly difficult patients are those with little or no history of dyspepsia who have brisk recurrent bleeding and in whom nothing may be seen or felt initially at laparotomy. Professor Bruce and Mr. Dudley have shown that " blind gastrectomy " gives real help in stopping bleeding, but there is no need to keep it blind. A wide gastrostomy or duodenostomy enables the not uncommon high gastric ulcer or the post-bulbar duodenal ulcer to be detected and dealt with appropriately. In a few of these persistent bleeders no ulcer may be found after the most careful search and the bleeding is in fact diffuse from an acute gastritis. Partial gastrectomy seems to be the best course for them.

Department of Gastro-Enterology,
Central Middlesex Hospital,
London, N.W.10. F. AVERY JONES.

SIR,—I was disappointed that Professor Bruce and Mr. Dudley (Dec. 5) made no reference, in their discussion of gastroduodenal hæmorrhage, to the adrenaline-'Stypven' method of treatment and case selection.

I, and some of my colleagues, have used this method since it was described by Brandon,[1] and we have no doubt of its value. It will arrest hæmorrhage in a high proportion of cases of acute ulcer, while if bleeding continues after the treatment immediate operation is indicated—and will almost invariably disclose a chronic ulcer or other "surgical" condition. It is completely safe, and is also extremely effective as a treatment of postoperative bleeding from the suture line. It is the only medical *treatment* (as opposed to supportive measures) for gastroduodenal hæmorrhage, and if properly used it will diminish the need for gastrectomy—which is a good operation for chronic peptic ulcer, but an absurd remedy for an acute erosion.

Professor Bruce and Mr. Dudley's figures emphasise two important points:

(1) That small or superficial chronic ulcers may be extremely difficult to find, and

(2) That emergency gastrectomy is dangerous. Elective gastrectomy is a mildly tedious and entirely safe procedure, whereas operation in the presence of massive hæmorrhage continues to be an unsafe, uncertain, and complication-ridden enterprise. Let us avoid it when we can.

Barnet General Hospital. V. J. DOWNIE.

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—When I was writing an M.D. thesis on Congenital Defects Caused by Virus Diseases Before Birth, in 1947, Prof. Ida Mann very kindly allowed me to cite two of her hitherto unpublished cases of defects following influenza in pregnancy. I hope she will forgive me for quoting them again here.

CASE 1.—A boy, born in South Africa on Sept. 28, 1935. In July, 1935, his mother had virus-A influenza. She was ill for 3 weeks, during which time she had a threatened abortion. The child had a curious diffuse pigmentation of the retina, with night-blindness and slight diminution of visual acuity.

Here (says Professor Mann) there was obviously a developmental defect of the optic cup. The infection was coincident with the time of finishing of differentiation of the outer layers of the cup.

CASE 2.—A boy, born on Sept. 20, 1946. The mother had influenza and possibly mumps at the same time when 6 weeks pregnant. The child was born with a curious face, one palpebral aperture being much wider than the other; there was also a slight facial palsy, a malformation of the end of the nose, and a heart lesion. His head was small, with open fontanelle and shallow orbits, so that the eyes protruded slightly. There was no cataract and the eyes themselves were normal.

I looked up the published work at the time and found that Dogramaci and Green [2] had recorded two examples of congenital patency of the interventricular septum in children whose mothers had influenza in the 2nd and 3rd months of pregnancy. Otherwise I could find only one relevant published observation—that of Bull,[3] who put the incidence of miscarriage in women who contracted influenza during pregnancy at 35–60%, surely far too high a figure?

It will be interesting to hear what Dr. Coffey and Professor Jessop (Nov. 28) find in their cases when they examine them later. I suppose a good many more children may then be found to have deafness, heart lesions, or even cerebral palsy, conditions which cannot often be detected at birth?

A curious feature of their present findings was that the incidence of malformations in the mothers who had influenza in pregnancy was very much higher (3·9% and 4·4%) in the cases examined at the National Maternity and Coombe Lying-in Hospitals than at the Rotunda (2·7%), but that the incidence of malformations in the controls was much higher in the Rotunda (2·7%, the same as in the influenza group) than in the other two hospitals (1% and 0·7%). Is this a mere coincidence—this kind of inquiry always bristles with them—or may there have been a lot more unnoticed influenza among the Rotunda mothers?

Tonbridge, Kent. E. CLAYTON-JONES.

FOLIC-ACID DEFICIENCY IN PREGNANCY

SIR,—May I support the advocacy by Mr. Francis and Dr. Scott (Dec. 5) of routine folic acid for anæmic pregnant women? A six-month acquaintance with midwifery and antenatal supervision was sufficient to bring me to the same opinion for essentially similar reasons.

I suggest that if more doctors were to perform hæmoglobin estimations very late in pregnancy many would find that severe anæmias are much more common then they have imagined. The ill-effects of these anæmias are, of course, not ended by a safe delivery.

In my experience outside hospital, hæmoglobin estimations, if performed at all, are often only done once-for-all either at the first attendance or at some arbitrary date such as 32 weeks. Postpartum estimations are rare. Surely this is not good enough.

Redness of the face and the conjunctival mucosa can be grossly misleading indications of the hæmoglobin level, but they are heavily relied upon.

Stafford. J. H. E. BAINES.

STANDARDS FOR HEIGHT AND WEIGHT OF BRITISH CHILDREN FROM BIRTH TO MATURITY

SIR,—Standards for children's heights and weights at each age are of use not only to pædiatricians and other specialists but also to general practitioners, school medical officers, physical educationalists, and others concerned with the welfare of children. Such standards are only useful if they provide an adequate means of assessing the position of a given child within the whole range of healthy children, and of seeing rapidly if abnormality should be suspected. Last year one of us presented a series of charts based on the best figures at present available, and giving the 3rd, 10th, 25th, 50th, 85th, 90th, and 97th percentiles for height and weight at all ages from birth (or one month in the case of length) to maturity.[1] These charts have now been redrawn in an improved version and made available commercially.

There are three charts to cover the whole age range; one from 0 to 3 (nude weight and supine length), the second from 2 to 10 (nude weight and standing height), the third from

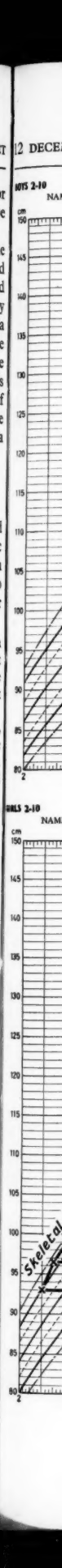
1. Brandon, W. J. M. *Lancet*, 1956, i, 360.
2. Dogramaci, I., Green, H. *J. Pediat.* 1947, **30**, 295.
3. Bull, C. *Arch. Pediat.* 1945, **62**, 289.

1. Tanner, J. M. *in* Modern Trends in Pædiatrics (edited by A. Holzel and J. P. M. Tizard). London, 1958.

CAPTIONS TO ILLUSTRATIONS (*facing*)

Fig. 1—Chart of normal boy from 3½ to 10 years.

Fig. 2—Chart of girl with presumed pituitary dwarfism. Circles plot height and weight on the basis of chronological age, and crosses height and weight on the basis of skeletal age. Note that the child is within the normal height and weight limits for skeletal age, indicating that the main effect is retardation of growth rather than diminutive size itself.



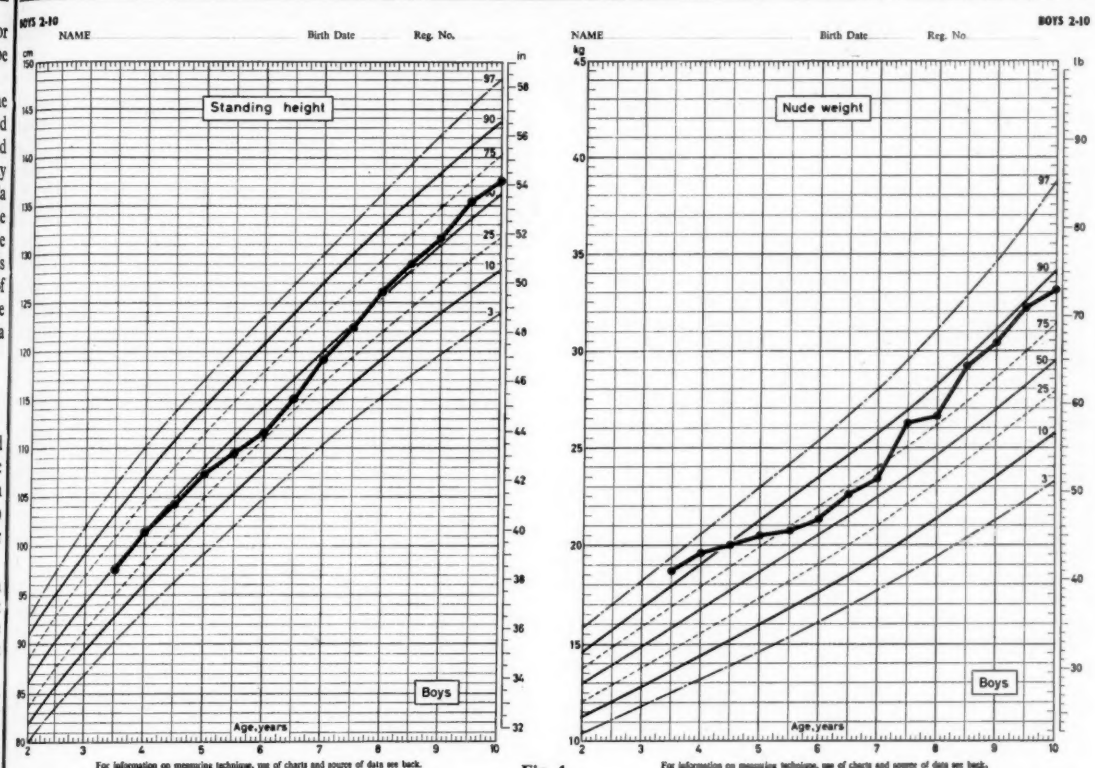

BOYS 2-10
NAME
Birth Date
Reg. No.
Standing height
Boys
Age, years
For information on measuring technique, use of charts and source of data see back.
BOYS 2-10
NAME
Birth Date
Reg. No.
Nude weight
Boys
Age, years
For information on measuring technique, use of charts and source of data see back.

Fig. 1.

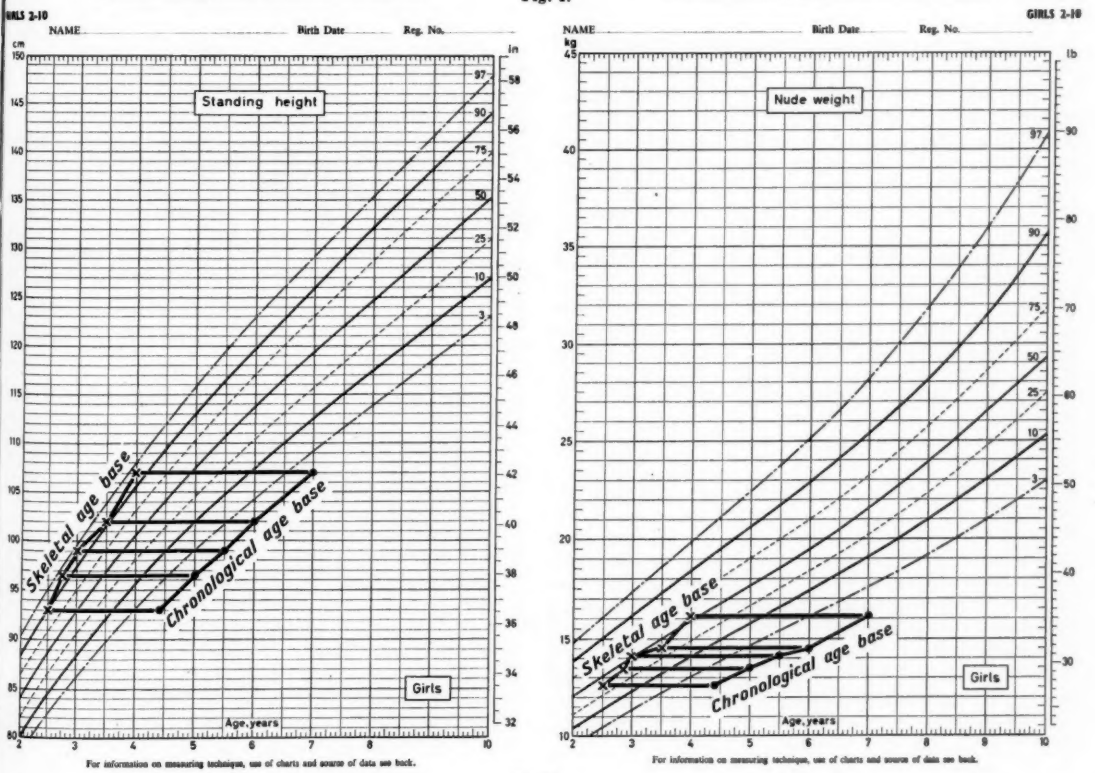

GIRLS 2-10
NAME
Birth Date
Reg. No.
Standing height
Skeletal age base
Chronological age base
Girls
Age, years
For information on measuring technique, use of charts and source of data see back.
GIRLS 2-10
NAME
Birth Date
Reg. No.
Nude weight
Skeletal age base
Chronological age base
Girls
Age, years
For information on measuring technique, use of charts and source of data see back.

Fig. 2.

9 to 18. The charts are printed on a single folding card of a size suitable for most hospital folders, with different colours for boys and girls. The inside two pages are the charts for height and weight. The front outside page is a record form for writing in, at each visit of the child, his age, height, weight, height percentile, weight percentile, and, where relevant, his skeletal age and ratings of secondary sex character development. The back outside page gives details of how height, supine length, and weight should be measured; how the charts should be used; the source of the standards; and the description of ratings for adolescent development. It also discusses briefly the deviation from the standard to be expected of any individual at adolescence, together with the means of overcoming this by using skeletal age rather than chronological age as a base. The charts are printed in grey so that blue-black ink recordings show up well on them, and height and weight are given in both metric and English systems.

The record of a normal child followed for ten years at the Harpenden Growth Study is shown in fig. 1; and in fig. 2 of a case of pituitary dwarfism, where height and weight are plotted against skeletal as well as chronological age.

We are greatly indebted to various colleagues for their constructive criticisms of the charts, and particularly to Prof. Alan Moncrieff, Dr. G. H. Newns, and the members of the medical committee of The Hospital for Sick Children, Great Ormond Street.

The charts may be obtained from J. Collard & Sons, 24, Litchfield Street, London, W.C.2. The cost of 3000 charts is £36 (approximately 3*d.* each), of 600 charts £16 10*s.* (approximately 6*d.* each), and of smaller numbers somewhat higher per card.

University of London, Institute of Child Health; and Harpenden Growth Study.
J. M. TANNER
R. H. WHITEHOUSE.

USE OF THE TERM "SUPERFEMALE"

SIR,—The word "superfemale" applied to individuals of the fly drosophila with three X chromosomes and two sets of autosomes (3X 2A), has always had unsuitable connotations. It is true that in terms of the balance theory of sex determination in drosophila where 1X 2A is male and 2X 2A is female, the constitution 3X 2A signifies a greater dose of female determiners than that in normal females. Developmentally, however, the expression of femaleness reaches its upper limit in normal 2X 2A individuals, and 3X 2A "superfemales" are poor female-type specimens with hypoplastic sterile ovaries and malformed wings and eyes. The majority die as larvæ or pupæ.

The inappropriateness of the term "superfemale" is emphasised by the discovery of a human 3X 2A individual whose primary and secondary sex characters are underdeveloped.[1] It would seem to be desirable to apply some term other than superfemale to the abnormal 3X 2A women. The word *metafemale* is here suggested (*meta*, beyond). This word is also being applied to a recently discovered new type of female in drosophila, of the chromosomal constitution 4X 3A, to be described by Mr. Justin Frost.[2]

The neutral quality of the word metafemale has the additional advantage that it is applicable to different situations of sexual differentiation. Unlike drosophila the influence of the X chromosome on sex determination in the human is not known. In drosophila, the absence in the Y chromosome of a gene, or genes determining maleness, made it possible to assign female determining tendencies to the X chromosome since 1X (no Y) individuals are male and 2X individuals female. In man there is no more than a suggestion of a similar property of the X chromosome in the gynæcomasty of some XXY Klinefelter males in contrast to normal XY males, and it is doubtful whether this localised effect on a secondary sex character should be regarded as evidence of genetic intersexuality. Moreover, in man, both 1X no Y and 2X individuals are females the former ones belonging to the hypoplastic Turner type. The term "metafemale" is therefore not only descriptive of the phenotype as beyond normal but avoids the unproven implication that a 3X person is at least genetically more female than a 2X person.

It has been stated above that so-called superfemales of drosophila are not only abnormal in their sex organs but also in parts unrelated to sex. This is a result of the imbalance in development caused by those genes located in the X chromosomes which have nothing to do with sexual differentiation. It would not contradict the designation of human 3X 2A individuals as metafemales if defects were observed outside of those of the sex organs. Indeed the lower than average mentality [3] of the metafemale described by Jacobs et al. may be another result of her abnormal chromosomal constitution.

University of California, Berkeley, California.
CURT STERN.

ACCIDENTAL INHALATION OF DISPERSER CARTRIDGE

SIR,—Most readers will be familiar with the 'Lomulizer' apparatus for inhalation therapy through recent advertisements. I should like to draw attention to a danger in the use of this apparatus which I have recently encountered.

A patient with severe chronic bronchitis was preparing to insert a cartridge into the lomulizer; he dropped the cartridge and unknown to the patient the cartridge fell into the mouthpiece of the lomulizer where it was not easily noticed. After searching unsuccessfully for several minutes the patient inserted another cartridge and inhaled; the inhalation together with the air pressure from the rubber bulb shot the intact first cartridge into his mouth and down his trachea. Because of his subsequent severe coughing attack the patient called his family doctor who rapidly assessed the situation correctly. The patient was sent into hospital and later that day I bronchoscoped him and removed the intact cartridge from his left main bronchus.

One can foresee this situation occurring again as the cartridge fits very neatly into the mouthpiece of the apparatus.

West Norwich Hospital, Norwich.
A. H. C. COUCH.

PARTIAL NEPHRECTOMY

SIR,—I notice that the authors of a recent article [4] on this subject do not regard the guillotine technique as safe. They do not say what risk they have in mind, but presumably it is hæmorrhage. If so, do they believe that the apposition of flaps after a wedge excision adds any security to the direct hæmostasis which is a sine qua non in any type of partial nephrectomy? Surely apposition of this order would necessitate suturing under tension—dangerous because the sutures would inevitably cut out, or the enclosed renal tissue necrose?

The objections to wedge excision leaving anterior and posterior flaps are (1) technical, though this does not count for much; (2) the flaps are of uncertain viability, especially towards their margins; (3) the flaps do not adhere; (4) the flaps have no excretory function, being largely deprived of their tubules.

1. Jacobs, P. A., Baikie, A. G., Court Brown, W. M., MacGregor, T. N., MacLean, H., Harnden, D. G. *Lancet*, Sept. 16, 1959, p. 423.
2. *Proc. Nat. Acad. Sci. U.S.A.* 1960 (in the press).
3. *Lancet*, Sept. 26, 1959, p. 448.
4. Gow, J. G., Cosbie Ross, J., Hill, C. A. St. *Lancet*, Nov. 7, 1959, p. 769.

To turn to another point. Proximal ligation of vessels is always a chancy business. In this operation it may devascularise too much or too little of the lower pole, and so prove either dangerous or useless. Certainly with a wedge excision it cannot be easy to judge the extent of devascularisation. Is it not safer to ligate only such vessels as are divided when the excision reaches the hilum?

Admittedly the number of guillotine cases reported [5] by me was small—10 in all—but I have added another 4 since, and now Murphy in a personal communication to Parry and Finelli [6] mentions a further 21 with satisfactory results. The total is still small, but may increase as time goes on.

London, W.1. STEPHEN POWER.

PROPHYLAXIS IN THROMBOEMBOLISM

SIR,—In your leading article last week you were good enough to mention the paper by Dr. Gallagher and myself in the same issue of *The Lancet*. You referred to 2 cases of fatal *hæmorrhage* in the series of patients given prophylaxis with phenindione. I am pleased to say that this is an error on your part, because there were no such cases. Presumably you meant to refer to the 2 cases of fatal *pulmonary embolism* which occurred after prophylaxis with phenindione had been stopped. In the trial, the absence of serious hæmorrhagic complications was noteworthy.

May I comment on another point? You build a superstructure of argument on the hypothetical concept of a link between "trauma, thrombosis, and the tendency to sudden hæmorrhage". In my opinion the concept is fallacious because the premise is untrue. Hæmorrhage after injury, massive or otherwise, has no connection with deep-vein thrombosis in the lower limbs. Bleeding after injury always has a local cause, although of course it can be more serious or extensive if there is an underlying hæmorrhagic diathesis like hæmophilia or scurvy. Bleeding into or from an injured area is due to torn blood-vessels; whilst the occasional cases of melæna or hæmatemesis which usually occur days or weeks after trauma are (almost) always due to peptic ulceration, antedating or complicating trauma. The danger of bleeding from peptic ulcers is of special importance in relationship to our proposal for prophylaxis with phenindione against venous thrombosis and pulmonary embolism; it requires special precautions, but that is another story.

Birmingham Accident Hospital. SIMON SEVITT.

SPECIFIC TUBERCULIN REACTION

SIR,—We were particularly interested to read your leading article of Nov. 14 on the investigation carried out by the Medical Research Council into the specificity of weak tuberculin reactions, as our own experience has been at variance with the opinions expressed by Palmer.[7]

Approximately 12½% of new recruits to the staff of our sanatorium fail to react to 10 tuberculin units (T.U.) but react to 100 or 200 T.U. of P.P.D. These weak reactors do not develop primary tuberculosis, whereas in pre-B.C.G. days tuberculin-negative staff converted to positive after an average of 4·4 months, and about 10% of the convertors developed clinical primary tuberculosis.[8] At this rate we should have had about 1 case of tuberculosis a year from the weak reactors. In fact there has been 1 case in 25 years. These findings support the view that reactions to 100 or even 200 T.U. are specific.

The M.R.C. is to be congratulated on restoring our faith in the value of the tuberculin test.

Cheshire Joint Sanatorium, Market Drayton, Salop. A. C. PENMAN D. H. ROXBURGH.

5. *ibid.* 1958, ii, 1257.
6. Parry, W. I., Finelli, J. F. *J. Urol.* 1959, **82**, no. 5.
7. Palmer, C. E. *Amer. Rev. Tuberc.* 1953, **68**, 678.
8. Edwards, P. W., Penman, A. C. *Lancet*, 1945, i, 429.

ORTHO-CRESYL PHOSPHATE POISONING

SIR,—The gravity of the mass outbreak of tri-ortho-cresyl-phosphate (T.O.C.P.) poisoning in Morocco must be our excuse for an intrusion into fields special to others; the outbreak has prompted us to put forward a hypothesis formulated during our study of an earlier outbreak.[1]

In T.O.C.P. poisoning, it is widely agreed that the essential lesion is demyelination of the peripheral nerves, the anterior roots, the columns of Goll, and the lower pyramidal tracts. Clinically, there is a delayed onset of motor paralysis of the limbs, with a slighter and transient sensory loss.

T.O.C.P. belongs to the group of anticholinesterases and it is an irreversible cholinesterase inhibitor.

Cholinesterase inhibition.—Experimentally, its main effect is to depress pseudocholinesterase levels, while its effect on true cholinesterase is slight. The organic phosphorus compounds, 'Mipafox' and possibly 'Parathion', also produce a delayed paralysis and D.F.P. has produced a similar effect in chicks. Mipafox and parathion, however, depress both true cholinesterase and pseudocholinesterase levels, while D.F.P. depresses mainly true cholinesterase.

Although the delayed motor paralysis of T.O.C.P. is very similar to that of mipafox, patients poisoned by mipafox suffer acute cholinergic effects immediately after ingestion of the poison. In T.O.C.P. poisoning the only possible equivalents are the inconstant and usually mild gastrointestinal upsets which are sometimes reported during the latent period. The symptoms of neuromuscular block which occur in mipafox poisoning, in particular fatigability, spasms and twitching with exercise,[2] are not found in T.O.C.P. poisoning. Occasionally, patients in our series reported sudden falls immediately preceding the onset of paralysis (the patient falls and rises again two or three times, then walks again for some yards), a symptom which could be related to block, but this phenomenon was variable and short-lived. Symptoms which resemble nicotine-like cholinergic effects may, however, accompany T.O.C.P. poisoning. In our cases muscular cramps were always present at the time of onset and muscular fibrillation has been reported.[3] But these symptoms do not occur at the time of ingestion when the cholinergic effects would be expected, but after a latent period at the time of onset.

Thus in T.O.C.P. poisoning the absence of the usual cholinergic symptoms at the time of ingestion of the poison, the fact that true cholinesterase levels are not depressed, the presence of sensory changes, and the distribution of demyelination in specific tracts make untenable any theory of simple anticholinesterase effects, such as that suggested by Koelle and Gilman.[4]

Pseudocholinesterase and demyelination.—The paralysis is probably directly related to demyelination. It has been suggested that antipseudocholinesterase activity might cause the demyelination,[5] but Paton [6] points out that antipseudocholinesterases other than T.O.C.P., mipafox, and parathion do not cause demyelination, while with these three poisons the depression in pseudocholinesterase levels is not concurrent in time with the demyelination. In T.O.C.P. depressed pseudocholinesterase levels would be expected shortly after ingestion

1. Susser, M. W., Stein, Z. *Brit. J. industr. Med.* 1957, **14**, 111.
2. Bidstrup, P. L., Bonnel, J. H., Beckett, A. G. *Brit. med. J.* 1953, i, 1068.
3. Hunter, D., Perry, K. M. A., Evans, P. B. *Brit. J. industr. Med.* 1944, **1**, 227.
4. Koelle, G. B., Gilman, A. *J. Pharmacol.* 1949, **95** (*Pharm. Review*, 166).
5. Earl, C. J., Thompson, R. H. S. *Brit. J. Pharmacol.* 1952, **7**, 261.
6. Paton, W. D. M. *in* Lectures on the Scientific Basis of Medicine, 1953-54; p. 105. London, 1954.

of the poison, but signs of paralysis appear only after a latent period. Another important argument against a specific anti-pseudocholinesterase effect on myelin is the fact that D.F.P., which does cause demyelination, is not associated with a prolonged depression of pseudocholinesterase.[7] On the other hand, Earl and Thompson[5] maintain that the degree of pseudocholinesterase depression caused by T.O.C.P. in vivo can be related to species resistance to paralysis—e.g., the albino rat is resistant to pseudocholinesterase depression and to paralysis; hens show pseudocholinesterase depression and are easily paralysed.

Thus it seems that demyelination causes the paralysis. The demyelination may result, as Paton argues, from the action common to T.O.C.P., mipafox, parathion, and perhaps D.F.P., against an enzyme, possibly pseudocholinesterase but more likely some other, which is concerned in the nutrition of myelin.

An extension of this hypothesis has been suggested to us by W. D. Stein. Lecithin, an important constituent of myelin, is related in chemical structure to T.O.C.P., both compounds being esters of phosphoric acid. Hence, T.O.C.P might interfere with myelin formation by acting as an anti-metabolite on an enzyme system concerned in the metabolism of lecithin. It would be of interest to investigate whether the pseudocholinesterase of the medullary sheath has any action on choline esters of phosphoric acid. If this was found to be the case, the connection between pseudocholinesterase inhibition and demyelination would be strengthened. Alternatively, T.O.C.P. may be inhibiting an enzyme other than pseudocholinesterase concerned in the metabolism of lecithin. With regard to this, it is suggestive that the cholinesterase inhibitor, eserine, has been reported to have an inhibitory effect on intestinal lecithinase.

Department of Social and Preventive Medicine, University of Manchester.

MERVYN SUSSER
ZENA STEIN.

CHROMOSOME COMPLEMENT IN PARENTS OF PATIENT WITH GONADAL DYSGENESIS (TURNER'S SYNDROME)

SIR,—It is generally assumed that the chromosome abnormalities recently observed in mongolism and in Klinefelter's and Turner's syndrome are likely to arise from non-disjunction during parental gametogenesis. While direct proof of this concept is difficult to obtain, it seems worth while to try and obtain evidence which would exclude alternative explanations.

One such possibility is that either parent of the affected individuals has a chromosome abnormality which may be directly transmitted to a proportion of the offspring. The observation[8] that mouse females with a sex chromosome constitution of the XO type are occasionally fertile further justifies the search for an equivalent situation in man. This has been excluded in the family of a case of Klinefelter's syndrome in which a normal somatic chromosome complement in both parents was found.[9]

We obtained sternal-marrow samples from the parents of a typical case of Turner's syndrome, a 15-year-old girl, whose bone-marrow cells in culture displayed a complement of 45 chromosomes and whose sex chromosomes were interpreted as being of the XO type. The mother was 21 and the father 23 years old at the birth of the patient.

The marrow cells were continuously cultured in vitro according to a technique described elsewhere.[10] The somatic karyotype and the sex chromosome constitution were apparently normal in both parents. The chromosome counts were constantly 46 and the sex chromosomes were interpreted as being of the type XX in the mother and of the type XY in the father.

A more detailed report will follow.

Institute of Medical Genetics, University of Uppsala, and Pædiatric Department, Central Hospital, Eskilstuna, Sweden.

M. FRACCARO
K. KAIJSER
J. LINDSTEN.

ADAPTATION IN CALCIUM ABSORPTION

SIR,—I do not wish to anticipate work of mine which is about to appear in various publications,[1–4] but I feel compelled to correct a misapprehension in Dr. Kendall's letter of Dec. 5. It has been recognised since Pommer's day[5] that the wide osteoid borders of osteomalacia are not due to decalcification of bone but to failure of calcification of new bone, usually due to a reduction in the product of calcium × phosphate in the serum.[6] Diets sufficiently low in calcium inevitably produce negative calcium balance.[7] When such diets are fed to animals, mineral is of course removed from the skeleton, but matrix is also removed pari passu[8] and the result is osteoporosis.[9] I can see no good reason why the same should not be true in man.

Department of Medicine, Western Infirmary, Glasgow.

B. E. C. NORDIN.

CHRONIC DIARRHŒA DUE TO SENSITIVITY TO SERENIUM

SIR,—Serenium is an azo dye (2-4-diamino-4-ethoxy-azobenzene) which was first introduced into therapeutics by Ostromyslensky in 1930. The azo dyes were discovered as antiseptic and antibacterial agents as early as 1908 by Gelmo.[10] In 1926, Ostromyslensky[11] combined the azo dye with pyridine, a red dye, and since then serenium has been used in many preparations with pyridine and as a urinary antiseptic and analgesic.[12] Little is known about sensitivity to serenium itself and nothing could be found in the literature concerning it; but sensitivity to the azo dyes is mentioned, the most prominent effect being methæmoglobinæmia.[13–14]

A man aged 60 was given serenium (4 tablets of 0·1 g. daily) for prostatic inflammation. He developed intractable diarrhœa (5–6 times daily). The stools did not contain mucus or blood, and microscopical examination revealed no abnormalities. The diarrhœa was resistant to intestinal antiseptics, such as phthalylsulphathiazole and the quinoline compounds, and to symptomatic treatment with codeine phosphate. When the serenium was stopped after two months, the diarrhœa stopped. Two other opportunities arose, several months later, to confirm the first observation, when the patient had the same drug in smaller doses (1 or 2 tablets per day), and other preparations containing serenium. On these occasions diarrhœa recurred: it failed to respond to antihistamine drugs and stopped only when these drugs were withdrawn.

Department of Medicine, Alexandria University.

M. ESSAM FIKRY.

7. Davison, A. N. *Brit. J. Pharmacol.* 1953, **8**, 212.
8. Welshons, W. J., Russel, L. B. *Proc. Nat. Acad. Sci. U.S.A.* 1959, **45**, 560.
9. Jacobs, P. A., Strong, J. A. *Nature, Lond.* 1959, **183**, 302.
10. Fraccaro, M., Kaijser, K., Lindsten, J. *Ann. hum. Genet. Lond.* (in the press).

1. Nordin, B. E. C. *Prog. clin. Endocrin.* **2** (in the press).
2. Nordin, B. E. C. *Clin. Orthopæd.* (in the press).
3. Nordin, B. E. C. New Lankenau Hospital Symposium on Bone Metabolism (in the press).
4. Nordin, B. E. C. *Surgo* (in the press).
5. Pommer, G. Rachitis und Osteomalacie. Leipzig, 1885.
6. Howland, J., Kramer, B. *Amer. J. Dis. Child.* 1921, **22**, 105.
7. Albright, F., Bauer, W., Aub, J. C. *J. clin. Invest.* 1929, **7**, 75.
8. Carttar, M. S., McLean, F. C., Urist, M. R. *Amer. J. Path.* 1950, **26**, 307.
9. Crawford, J., Gribetz, D., Diner, W. C., Hurst, P., Castleman, B. *Endocrinology*, 1957, **61**, 59.
10. Gelmo, P. *J. prakt. chem.* 1908, **77**, 369.
11. Ostromyslensky, I. I. Scientific Basis of Chemotherapy. New York, 1926.
12. Goodman, L. S., Gilman, A. The Pharmacological Basis of Therapeutics. New York, 1943, 1956.
13. Meyler, L. Side-effects of Drugs; p. 250. Amsterdam, 1952.
14. Micks, R. H. Essentials of Materia Medica; p. 328. London, 1950.

LEAF PROTEIN AS HUMAN FOOD

SIR,—Mr. Pirie's article of Nov. 28 is very valuable. Some of the malnourished people are already making use of a variety of leaves, but it is a food that has little prestige value among many of these people, and has been largely ignored in the teaching propounded by foreigners, who have spent most of their time concentrating on the virtues of skimmed milk.

In Ghana there are over 40 varieties of green leaf which were commonly used for food. In Tanganyika and other parts of East Africa leaves are used fresh, and in some areas, such as Ugogo, they are preserved against the dry season, either as a dried powder kept in gourds, or boiled down and dried into a flat cake (rather resembling a small cowpat) and strung up in the cooking place. In the more provident families there were some of these cakes still being used, and crumbled into soups, stews, and relishes, even after the rains had started and fresh green stuff was plentiful.

A large variety of greens are used, including cassava, sweet potato, pumpkin, groundnut, a small mallow plant, and numbers of others. During the war the civilian prisoners in Singapore lived mainly on sweet-potato leaves and rice. There is no doubt that green leaves can be a valuable form of food, not only for the protein, but for iron, calcium, and possibly some traces of vitamins A and C.

Mr. Pirie says that "if 20 g. or more is eaten at one time, part of the chlorophyll escapes digestion in the gut and appears in the fæces". But is this not partly a question of habituation? Many people have found that even children will learn to accept, and apparently to absorb larger quantities.

This is a form of food which is already known and acceptable and is very often available, especially in rural areas. Many people have been in favour of encouraging the consumption of green leafy vegetables both in the fresh and in the dehydrated state. It is a subject which would repay further analysis, so as to further the use of those plants that have the highest food values.

The main difficulty is not the lack of research and of knowledge, but that in areas where this knowledge is most needed there are few hospitals or health centres and there are still fewer doctors and health visitors with adequate knowledge of pædiatrics or of clinical nutrition. Without doctors and health visitors it is difficult to ensure that foodstuffs are used correctly.

c/o School of Public Health,
American University of Beirut,
Lebanon. CICELY D. WILLIAMS.

SIR,—Mr. Pirie's most interesting article in your issue of Nov. 28 makes an eloquent plea for the utilisation of leaf protein as a human foodstuff. While full of admiration for the technological achievement I find myself doubtful of the practicability of this scheme in so far as south-east Asia is concerned.

Protein extraction from leaves clearly depends for economic success on the availability of very large quantities of waste or cultivated leaves with a high nitrogen content in just those countries where protein malnutrition is a serious problem. I suggest that such large amounts of leaves are not, in fact, readily available.

Let us examine the examples quoted by Mr. Pirie.

Papyrus may be dismissed at once as an Asian source, but water hyacinth is another matter. It is a serious weed in waterways but it tends to proliferate in areas where human settlement is sparse and access difficult. It has a low dry matter content and, when collected in heaps for transportation, it would decompose rapidly. In more settled areas it is cultivated on fish-ponds and fed to pigs whose dung and urine are returned to the ponds, thereby encouraging a vigorous growth of algæ on which fish are reared. Such a food chain needs no factory and, in Malaya, is responsible for a greater yield of edible protein per acre than any known form of dry-land agriculture.

In Malaya, at least, there is no such thing as waste leaves of sweet potatoes. The poorer people make soup of the young leaves and the tops are a major pig food. The leaves are, in fact, a more important crop than the tubers and special varieties have been selected which give maximum yields of green matter.

In countries such as Mauritius, where sugar-cane is the main cash crop, the leafy tops are stall-fed to cattle and they make an excellent fodder.

Banana leaf sheaths, together with the younger leaf blades, are fed to pigs by Chinese farmers. Older leaf blades, low in protein, are in demand as food wrappers.

Young leaves of tapioca (cassava) are used as a green vegetable throughout the East and the surplus of old leaves is relatively small at the time when the roots are harvested.

It seems doubtful that special crops would ever be grown for the extraction of leaf protein except in those countries which practise extensive mechanised agriculture. These are the countries where the standard of living is now above average and protein nutrition satisfactory. Experience in the East suggests that increasing population pressure on cultivable land leads to an intensive form of agriculture, with most of the best land devoted to crops grown for direct human consumption. In such conditions fodder crops disappear and most of the cattle are replaced by pigs which are fed on crop residues and the by-products of sea-fisheries.

Japan provides the classical example of an intensive agriculture dictated by land hunger. Her population relies largely on sea fish for their protein, with the balance provided by soya-bean products and similar crops.

No research on the nature and properties of vegetable proteins is ever wasted but a scheme for their factory extraction from leaves requires very careful scrutiny before it can be recommended with confidence to the so-called underdeveloped countries of the world. The first question which requires an answer is whether it would yield a greater weight per acre of digestible and palatable protein than pig and pond-fish farming.

Copdock,
near Ipswich, Suffolk. E. F. ALLEN.

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—May I answer Professor Owren's comment (Dec. 5) on my letter of Nov. 21? The following points provide practical as well as theoretical support to my claim that the thrombotest is not sensitive to Christmas factor.

(1) *Composition of the thrombotest reagent.*—Professor Owren says "Brain extract definitely does *not* contain Christmas factor". But we simply do not know! There is, however, no doubt that Christmas-factor *activity* (as I said in my letter) is therein.

The incorporation of a clotting-factor or its substitute in a reagent prohibits the utilisation of the latter in the estimation of this particular factor. An analogue to this is the use of cephalin (which is *not* platelet-factor 3) as a substitute for platelet activity in the thrombotest; otherwise, according to Professor Owren's argument, platelets should have been one of the constituents of the thrombotest reagent.

Another obscure point in the construction of the reagent is the need to add cephalin to animal brain which definitely *does* contain cephalin.

(2) *Sensitivity to Christmas factor and antihæmophilic globulin.*—In Professor Owren's letter, the sentence "It is well

known that tissue thromboplastin acts independently of the antihæmophilic factors . . ." seems to contradict another phrase, " Hæmophilic plasma gives a prolonged thromboplastin time with a dilute tissue thromboplastin . . .", by which he implies that it is dependent on antihæmophilic globulin. The independence is definitely due to the presence of Christmas factor and antihæmophilic-globulin *activities*.[1] The apparent " dependence " is due to Professor Owren's misinterpretation. This phenomenon, which is detected only at dilutions over 1:1000 (not 1:4 as in the thrombotest), has been thought to be due to an inhibitor [2] and *not* to sensitivity to antihæmophilic-globulin levels.

(3) *Results.*—10 patients with Christmas disease have been examined by me; the results were within normal (6 specimens) range. A patient with combined Christmas disease and slight factor-VII deficiency (one-stage prothrombin time of 15 sec.; normal control 12 sec.) gave 50% activity with the thrombotest. These findings give conclusive evidence regarding the insensitivity of the thrombotest to Christmas factor.

(4) *What is the value of the thrombotest?*—On replacing platelets with phospholipid (cephalin), the species specificity of plasma-thromboplastin becomes dependent on a serum factor [3] which, from the above results, would appear to be factor VII. Accordingly, I believe that by using an animal brain extract, the thrombotest has increased the sensitivity to factor VII and, in consequence, to prothrombin levels. This is substantiated by Professor Owren's fig. 4. The slope of the curve of the *one* sample examined is obviously an exaggeration of that seen in the P-P curve in the same figure. This suggests increased sensitivity to factor VII and prothrombin, the concentrations of which in this particular instance (precise amount and method of mixing the different proportions of the plasmas required are not indicated) is stated to be " *about* 20% in all samples tested ".

Contrary to Professor Owren's belief I did use platelets in the experiments [4] to which I referred, thus rendering untenable the point raised in his letter. In fact, I actually mentioned in the same paper, experiments which indicate that it is my belief that the clotting activities of phospholipid and platelets are not identical.

The Royal Infirmary,
Manchester. F. NOUR-ELDIN.

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—On the correspondence in your issue of Dec. 5 I will comment as briefly as possible.

(1) The question of what Pickering calls " unconscious digit preference " was considered in my paper. If we accept it as an explanation of the bimodal curves are we not then arguing thus: when the curve is unimodal it proves Pickering's hypothesis; when bimodal it proves nothing.

(2) Pickering rightly says that arterial pressure is the resultant of a large number of variables. This does not argue at all against the possibility that only one of these variables is disturbed in a certain defined group of hypertensives. Aldosteronism is an example and the hypertension it causes can be of very variable degree. A similar state of affairs (as yet undiscovered) could account for essential hypertension.

(3) Evidence in favour of there being two populations, in one of which the pressure rises only slightly with age, and in the other significantly, has been presented in papers by Thomson [6] and by Cruz-Coke [7] in addition to the data of Morrison and Morris.

(4) I would not agree that the curve in fig. 2 of Keen and Rose (Dec. 5, p. 1029) is unimodal.

(5) In answer to Smith (p. 1030) (*a*) a gene which has lethal effects in post-reproductive life will not be eradicated. It is no new discovery that hypertension shortens life. (*b*) One would expect the degree of hypertension of propositi (who have complained of symptoms) to be higher than those of their relatives (who have not).

Finally was it not a pity that Pickering should bring in Wilfred Trotter? Up to now, Morrison and Morris and I have been presenting evidence (not without bias perhaps) on which judgments may well differ. But as from now, belief in the doctrine of the Continuous Distribution is mental righteousness.

Department of Medicine,
The Royal Infirmary,
Manchester. ROBERT PLATT.

ANEURINE FOR CHRONIC COUGH

SIR,—I have been using large doses of aneurine (thiamine) in the treatment of chronic cough, whatever its cause.

In the past seven years I have prescribed large doses by mouth for varying periods (150–200 mg. in divided doses 3–4 times a day for adults and 100 mg. daily for children under 6). Less frequently, because of the possibility of reaction, I have prescribed aneurine by intramuscular injection (100 mg. daily on two or three successive days), followed by oral doses.

The observations recorded below are based on approximately 300 patients with chronic cough seen in private practice and clinics. The only criterion was that the patient had coughed for a long time. In 90% no acceptable cough remedy had been more than temporarily effective, and in the other 10% no medication was taken at all.

In the first group were the chronic coughs where the original cause, either because of delayed treatment or no treatment, had finally produced daily coughing spasms. Thus, in pertussis in children or in adults, there are many patients who continue to cough for months after the usual six weeks of the disease. Similarly, in primary atypical pneumonias, the cough can persist after the temperature, pulse, and general condition have returned to normal. This is a type of cough which is referred to as " useless cough " or, as Banyai calls it, " tussal insufficiency ".[1] In every case where the cough had persisted for weeks and months, the cough resolved completely within one to two weeks. When aneurine was given intramuscularly (100 mg. daily on two or three successive days) the results were even better: there was a sudden decrease in the coughing spasms and there was almost no need for subsequent oral thiamine.

The second group included cases in which chest X-rays were abnormal (e.g., chronic bronchitis with or without bronchiectasis, emphysema, or fibrosis) or in which X-rays were negative but there was a history of chronic irritative disease such as nervous cough or smoker's cough. The addition of large doses of aneurine to other treatment resulted in a striking improvement, but not necessarily complete control.

A woman had been coughing for two months without relief from codeine or its derivatives. A mass was seen fluoroscopically in the hilar region. 200 mg. of aneurine was given daily, and a week later the patient admitted that for the first time her cough had improved considerably and she could sleep easily, although some cough persisted. Bronchoscopy demonstrated a bronchogenic carcinoma.

A patient with chronic bronchial asthma and fibrosis, a heavy cigarette smoker, complained of coughing spasms at all times of the day. 200 mg. of aneurine daily by mouth, after a few weeks, improved his spasms and clinical condition so much that the lungs appeared clearer and the wheezing stopped. As long as he smoked, his cough, although better, continued.

Aneurine seems to improve only chronic " useless " coughing, and it is of no use in cough due to acute disease, which will limit itself anyway. It is, however, valuable for persistent

1. Biggs, R., Douglas, A. S., Macfarlane, R. G. J. *Physiol.* 1953, **122**, 554; Nour-Eldin, F., Wilkinson, J. F. *Brit. J. Hæmat.* 1956, **2**, 433.
2. Biggs, R., Macfarlane, R. G. *J. clin. Path.* 1951, **4**, 445.
3. Nour-Eldin, F., Wilkinson, J. F. *Quart. J. exp. Physiol.* 1957, **42**, 171.
4. Nour-Eldin, F. Fourth International Congress of Biochemistry; vol. 10, p. 138. Vienna, 1959.
6. Thomson, K. J. Proceedings of the 38th Annual Meeting of the Medical Section of the American Life Convention, 1950.
7. Cruz-Coke, R. *Acta gen. stat. med.* 1959, **9**, 207.

1. Banyai, A. L. *J. Amer. med. Ass.* 1952, **148**, 501.

cough which has proceeded beyond the capacity of the patient's resistance to stop naturally.

Sometimes oral or intramuscular aneurine produces such improvement in cough that the cause is "masked". Patients feel better, and they may ignore an important follow-up.

Intramuscular aneurine carries a danger of shock-like reaction, and must be used carefully. Large daily doses by mouth did not produce sensitivity in any patient, even after many months. It has been reported,[2] however, that large doses over long periods do cause side-effects.

Of the action of aneurine, Sebrell and Harris [3] say:

"It blocks transmission of nerve impulses through the superior cervical ganglion. Besides its ganglionic depressant action at large doses, thiamine, in still larger doses, depresses the transmission of impulses to the skeletal muscle at the neuromuscular junction. In accord with this curare-like action, it has been found to depress the response of the skeletal muscle to acetylcholine."

Such an action could explain my findings.

Flushing,
New York. JOSEPH G. LEVACK.

CEREBRAL REGULATION OF SODIUM EXCRETION

SIR,—In a series of observations [4] in dogs with crossed circulation we demonstrated that intracarotid injection of hyperosmotic sodium-chloride solution was followed by a rise of urinary sodium excretion. The head of the acceptor animal being isolated from its trunk, this effect cannot be brought about but by neural pathways.

The intracarotid injection of hyperosmotic sodium-chloride solution is followed by endogenous liberation of antidiuretic hormone (A.D.H.). The possibility arose that A.D.H. may act on some part of the central nervous system in promoting this sodium excretion.

To elucidate this question we performed 20 crossed circulation experiments and investigated the effect of intracarotid injection of 0·1 unit of posterior-pituitary extract ('Piton') on sodium excretion. A statistically significant rise in sodium excretion followed. In several clearance periods the rise in sodium excretion was achieved by diminished tubular reabsorption of sodium.

Our results will be published in detail in *Acta physiologica hungarica*.

1st Medical Department, University Medical School, Budapest; M. FÖLDI
Institute of Physiology, University Medical School, Budapest; A. G. B. KOVÁCH, M. PAPP
Institute for Experimental Medicine, Hungarian Academy of Sciences, Budapest. E. KOLTAY, L. SOMLYAI.

ORPHENADRINE AND PHENOTHIAZINES IN SCHIZOPHRENIA

SIR,—Blair et al.[5] advocated the occasional use of benzhexol with phenothiazines in the treatment of schizophrenia. Freyhan,[6] in his evaluation of trifluoperazine, states: "Some of these compounds, notably 'Disipal', are mild stimulants, or exert some psychotropic effect of their own." There are thus grounds for believing that some anti-parkinsonian agents further the therapeutic effects of phenothiazines, for one of various reasons: (*a*) potentiating the psychotropic effect; (*b*) exerting an independent psychotropic action; (*c*) abolishing the psychomotor retardation of a phenothiazine-induced pre-parkinsonian state.

In order to satisfy ourselves that orphenadrine ('Disipal') had the action that Freyhan claims, we conducted a small trial on long-stay schizophrenics who were well stabilised on phenothiazines and had made a good adjustment to hospital life, but who were still incapable of independent existence outside hospital.

Using the double-blind cross-over method, one month each way, giving one 50 mg. orphenadrine tablet or its neutral facsimile three times a day with the phenothiazine, our results with 20 male patients were:

On *active* tablet: 4 much improved, 4 moderately, 4 slightly, 8 not improved, 0 worse.

On *placebo*: 1 much improved, 1 moderately, 0 slightly, 15 not improved, 3 worse. $\chi^2 = 10{\cdot}96$; $P = 0{\cdot}001$.

It is our experience from personal communications that many psychiatrists oppose the use of anti-parkinsonian agents with phenothiazines. When faced with extrapyramidal symptoms, some will reduce the dosage to a level that may be below the therapeutic, or discontinue an effective agent.

In our view, orphenadrine has two virtues: (1) it enhances the therapeutic effect of the phenothiazine; and (2) it obviates the occurrence of extrapyramidal symptoms.

Incidentally, this study supports the argument that any anti-parkinsonian agent given during a blind clinical trial of phenothiazines tends to invalidate the results.

Our thanks are due to Dr. G. A. Schmeidler, of the Camden Chemical Co. Ltd., for generous supplies of orphenadrine.

Herrison Hospital,
Dorchester, Dorset. R. H. BOARDMAN
A. G. FULLERTON.

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—Collapsed patients with ectopic gestation who have lost many pints of blood into the peritoneal cavity die usually of irreversible shock either during operation or very shortly afterwards. In Nigeria where there is only a limited blood-transfusion service in few centres, their chances of survival are slight. Other fluids merely dilute the remaining blood and diminish its oxygen-carrying power. I can recommend the following procedure:

Quickly transfer the patient to an operating-theatre and expose a large vein in the arm or near the ankle by quick dissection. The patient is in such a shocked state that an anæsthetic is not usually necessary. A large-bore needle is then inserted into the exposed vein.

The abdomen is opened rapidly under local anæsthesia. Collect as much blood as possible into sterile containers. Strain it through sterile gauze, the bleeding vessels having been clamped to stop further loss.

A large syringe (for example, 20 ml.) is used to reinject the strained blood into the circulation through the needle in the vein. The patient's general condition usually improves rapidly, and operation can be completed without anxiety.

Postoperative antibiotics are given to combat any contamination of the transfused blood. Further transfusion of other fluids is often unnecessary.

The following case illustrates the value of this method.

A married woman of 21 was admitted to the Maternity Hospital, Aba, on Dec. 11, 1958, complaining of severe vomiting. She had had nine weeks' amenorrhœa. The vomiting subsided; but two days later slight vaginal bleeding was discovered, and ten minutes later she collapsed suddenly. The abdomen was tender and distended. The pulse was very fast (108) and thready, and cold clammy sweat covered her body. She was constantly asking for water. A diagnosis of ruptured ectopic gestation was made, and immediate operation on an unfit patient was imperative. All attempts to get compatible donors failed, and there was no means of testing for rhesus incompatibility. In this dilemma the patient's general condition was getting worse every minute.

The method described above was used and the patient survived the operation uneventfully. Before the bleeding

2. Mills, C. A. *ibid.* 1941, **116**, 2101.
3. Sebrell, W. H., Jr., Harris, R. S. The Vitamins; p. 467. New York, 1954.
4. Kovách, A. G. B., Földi, M., Papp, N., Róheim, P. S., Koltay, E., *Lancet*, 1959, i, 338.
5. Blair, D., Brady, D. M. *J. ment. Sci.* 1958, **104**, 625.
6. Freyhan, A. F. Trifluoperazine; p. 204. Philadelphia, 1958.

points were secured she had already lost more than five pints of blood into her peritoneal cavity. Three months later she was quite healthy and her hæmoglobin was 80%.

This simple method could be applied by any doctor, with little or no assistance, in a remote hospital; and it could be used in other forms of intraperitoneal hæmorrhage. No transfusion set is necessary. No donor need be sought. No laboratory is needed. No fear of incompatibility need arise. And no time need be lost.

General Hospital,
Ministry of Health, Aba, Nigeria. A. A. AZIE.

REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—May I point out that Dr. Tuthill (Dec. 5) is wrong in stating that "Pages 152–155 of the Wolfenden report list all the witnesses". If he turns to page 7 (4) he will see that this is merely a representative list and "in addition to those named in that list, there are others, too numerous to be mentioned by name, who have helped us by tendering evidence, either written or oral". Among these were representatives of the three classes mentioned by Sir Heneage Ogilvie, but precious little notice was taken of them.

Mr. Walker (Dec. 5) does nothing to remind us that he started this correspondence by stating the case of a poor lad who committed suicide in Durham Prison and quoting Mr. Justice Elwes's comment on it. He does not tell us that this case was debated in the House of Commons (*Hansard*, Nov. 5, cols. 1195–96 and 1329–42, essential reading for anyone who wants to join in this fight) and that the Judge was as severely criticised for that comment as a Judge can be in a place where the justiciary is supposed to enjoy a perpetual close-time. Dame Irene Ward said she had reported the matter to the Lord Chancellor, that the Judge ought to apologise, and that it was unjust that people who could not defend themselves—the police who opposed bail and the magistrate and Judge in chambers who refused bail—should have to "stand under his caustic tongue when the facts have been incorrectly stated." Mr. Walker does not mention that the kernel of his complaint was maggoty.

It is the massive, soundly instinctive, and passionate opposition to the committee's first recommendation (and its corollaries, 2 and 3) on legalising homosexuality in adult males that prevent the other recommendations, which seem to me sane and humane, from being implemented.

Beckley, Rye. C. G. LEAROYD.

POSTOPERATIVE DIARRHŒA

SIR,—Mr. Schofield (Nov. 28) refers to an article of mine and raises several queries. He states that he is unable to see "how an obstructive lesion could cause intestinal hurry, especially as dilated loops of bowel were seen radiologically and at operation in all patients, which is surely good evidence of intestinal stasis".

In reply may I say that the intestinal hurry was proved by using methylene-blue tablets (gr. 2), and measuring the transit time through the bowel. Mr. Schofield reported that stagnation occurred clinically, but he gave no record of how this was determined.

The intestinal hurry in partial obstruction is the result of increased peristaltic activity due probably to an increase in intestinal content.

Evidence of increased activity is clearly obtained clinically by observation and auscultation. These incontrovertible clinical features occur when dilated loops are present in partial or complete intestinal obstruction. It is only at a later stage that stagnation (that is, ileus) supervenes.

The persistent diarrhœa in the patients mentioned in my article was cured by the removal of the partial obstruction.

To add another clear illustration of the effect of partial obstruction on bowel activity, may I refer to the ileal dysfunction described by Warren and McKittrick.[1] In these patients the increased peristalsis is clinically in evidence, and the diarrhœa is cured, not by antibiotics, but by gentle dilatation of the ileostomy.

London, W.1. J. J. SHIPMAN.

EFFECT OF TOLBUTAMIDE ON BILE SECRETION

SIR,—The oral treatment of diabetes in patients with liver damage is not yet generally accepted, though there is no conclusive evidence of deterioration in hepatic function during oral treatment.[2] Increased retention of bromsulphalein has, however, been reported.[3] Our aim was to study the effect of tolbutamide on bile secretion.

Albino rats, kept on a standard diet, were given for three days 50 mg. per 24 hours tolbutamide in solution (pH 7) through a gastric tube. The controls received the same quantity of water. On the third day cannulas were inserted into the common bile-duct under urethane anæsthesia. The bile produced was collected for three hours. As our experiments were comparative studies, and as there was no apparent hindrance to the bile flow (and there was no reason to suppose any other variable factors), the quantity of bile collected was taken as a measure of bile secretion. The results were as follows:

	Secretion (mg. bile per 100 g. body-weight per hour)	
	Tolbutamide	*Control*
No. of rats	13	15
Mean values of bile collected	179	137
Standard deviation	±43	±39
	$t \pm 3{\cdot}1$, $P < 0{\cdot}01$	

The findings indicate a significant increase in bile production after tolbutamide treatment.

We then wanted to determine the effect of tolbutamide in toxic liver injury. Rats were given 0·125 ml. of carbon tetrachloride subcutaneously 48 hours before the catheterisation of the bile-duct. In other respect the procedure was the same. The results were:

	Secretion (mg. bile per 100 g. body-weight per hour)	
	Tolbutamide	*Control*
No. of rats	8	11
Mean values of bile collected	119	60
Standard deviation	±52	±39
	$t \pm 2{\cdot}9$, $P < 0{\cdot}01$	

It seems that the decrease in bile secretion in carbon-tetrachloride intoxication can be prevented by tolbutamide.

Our results will be published in detail elsewhere.

2nd Department of Medicine,
University of Budapest. ANTAL KÁLDOR
GÁBOR POGÁTSA.

ENDOGENOUS HYPOGLYCÆMIA

THE letter on this subject in our issue of Nov. 14 should also have been signed by Dr. J. C. HAWORTH, and we much regret the inadvertent omission of his name. The third paragraph should have read:

"It has not been our experience, or the experience of some others,[3] that all cases of idiopathic hypoglycæmia respond well to treatment with corticotropin (A.C.T.H.) or corticosteroids. Conversely corticotrophin may relieve the hypoglycæmic symptoms of patients who are later found to have functioning islet-cell adenomata.[5] Thus response to corticotrophin is of no help in distinguishing the one type of case from the other."

3. *J. Pediat.* 1959, **54**, 116.
5. Roxburgh, R. C. *Lancet*, 1954, *i*, 1057.

1. *Surg. Gynec. Obstet.* 1951, **93**, 559.
2. Knick, A. *Klin. Wschr.* 1957, **35**, 812.
3. Warembourg, H., Stalnikiewicz, G. *Pr. méd.* 1959, **23**, 929.

Obituary

CHARLES JAMES CECIL EARL

F.R.C.P.I., D.P.M.

BECAUSE of ill health, Dr. C. J. C. Earl retired some six years ago from his appointments as medical superintendent of Monyhull and as lecturer on mental subnormality in the University of Birmingham. But even in this shortened working span his contributions to the study of mental deficiency were outstanding. He died on Nov. 29 in Dublin, where he was born just over 60 years ago.

His father was pathologist to the Richmond Hospital in Dublin, and he was one of four brothers who were all doctors. He was educated privately in Dublin and Birmingham and qualified in 1921. After serving as house-physician at the West London Hospital and as medical registrar at Salford Royal Hospital he entered the London County Council mental-health service, in which he was assistant medical officer at Tooting Bec. He had already become interested in mental deficiency, and in 1930 he took the D.P.M. with special knowledge in that subject. Soon afterwards he was appointed deputy medical superintendent to Caterham Hospital. In 1940 he was appointed medical superintendent of Monyhull Hospital, and while there he developed a research department to study the psychological problems of mental deficiency in its diagnostic and therapeutic aspects. He examined for the D.P.M. in Bristol and Manchester and he was for many years on the editorial panel of the *Journal of Mental Science*.

M. S., a colleague at Birmingham, writes:

"There is still a steady stream of original work coming from the research unit at Monyhull which owes its inspiration to Dr. Earl. His contributions to his chosen branch of psychiatry were internationally recognised; and his studies of tuberose sclerosis, mental testing of morons, and the elaboration of the psychograph for morons were examples of his original and inquiring mind. His psychiatric interests were not narrow, and he was among the first to introduce the study and use of the Rorschach test in this country. Though his illness curtailed his activities, he was, at his best, the most original and intelligent authority we had in mental deficiency. He was prevented from realising his full potential, but his contributions were substantial and lasting and are a fitting memorial."

Another colleague, E. N. B., describes him as a man of real ability combined with considerable originality.

"In his earlier years Earl was interested mainly in organic problems, but latterly he devoted himself to psychological aspects of mental deficiency and he paid special attention to Rorschach testing. There was no medical meeting which he did not enliven with his somewhat caustic wit. He had a measure of genius combined with a typically Irish perverseness."

W. M.-G., who visited Earl in his home in Dublin last September, relates:

"I found him as vivid, pugnacious, and interested in all matters of psychiatry as I had found him 25 years ago at Caterham Hospital when he was the host of some refugee colleagues from the Continent. The patients freely came to his room as to a fatherly friend, and this conveyed his whole life and personality. His devotion and great mental energy went into his work with mental defectives. Incessant and untiring observation and contact with his patients were the basis on which he built the model institute when he later became superintendent of Monyhull in Birmingham. There he was able to realise many of his highly original and independent ideas on education and treatment of these patients. His practical work was founded on a comprehensive knowledge of this often neglected branch of psychiatry, its neurology as well as psychology, its pædagogic and sociological problems. In his emphasis on the emotional problems of the subnormal, he was far ahead of his time and anticipated the reforms of the new Mental Health Act. He willingly acknowledged this progress from his detached retirement in which he wrote and concluded his *opus magnum* on the subnormal, to which we can look forward with great expectations."

ARCHIBALD GILPIN

M.D. Lond., F.R.C.P.

Dr. Archibald Gilpin, physician to King's College Hospital, died at his home in Dulwich on Nov. 29, while still in his early fifties.

He was educated at King's College, University of London, and at King's College Hospital. He was a brilliant student, winning many prizes in the medical school, and he was a fast and powerful wing three-quarter on the rugger field. He graduated M.B. with honours in medicine in 1929. After doing his house-appointments at King's he was awarded the Ferrier prize in neurology for his work on subarachnoid hæmorrhage and its relation to congenital aneurysms. In 1934 he was appointed University of London postgraduate travelling fellow and went to Freiburg, where he studied under Ludwig Aschoff.

On his return to King's he became Sambrooke medical registrar and later medical tutor, and he was appointed assistant physician and morbid anatomist in 1935. His experience under Aschoff showed itself in his teaching in the postmortem department which drew large numbers of students and postgraduates to his demonstrations. He was elected F.R.C.P. in 1938.

During the late war he carried on his hospital and private practice under difficult conditions, for his wife and young family had to be evacuated from Dulwich. In 1948 he was elected archivist to the Worshipful Society of Apothecaries and became the Harveian librarian of the Royal College of Physicians. Unfortunately his health broke down in 1949, and he was under treatment for his chest condition off and on for over two years; later he had to lead a somewhat restricted life and curtail his social activities, so that he tended to see less of his colleagues and friends.

J. L. L. writes:

"John, as friends called him, was a good general physician and an excellent clinical teacher, highly popular with his students and registrars. He was physician to the nurses for many years. He had a busy private practice and was much in demand among the local practitioners—many patients in south London are grateful to 'Dr. Gilpin'. He was interested in diseases of the blood and published articles on aspects of these disorders. His health precluded active sports, but he read widely and he was quite an authority on medical literature of the 17th and 18th centuries, his knowledge of French and German serving him in this. He was a keen collector of old medical books, and it was a pleasure to hear him discuss some new find, for which he had searched far and wide."

Dr. Gilpin leaves a widow with a daughter and two sons.

JOHN EDWARD GEORGE McGIBBON

O.B.E., M.B. Lond., D.L.O.

Mr. McGibbon, honorary otologist to the United Liverpool Hospitals, died on Oct. 25 at the age of 66.

He came of a medical family, and he was educated at Liverpool College and Liverpool University. In 1914 he joined the Army as a medical student, but in 1917 he returned to take his degree. After qualification he served in the Royal Navy as a temporary surgeon lieutenant. He was demobilised in 1919 and a little later returned to Liverpool to join his father, Dr. John McGibbon, in practice; but he soon decided to specialise in diseases of the ear, nose, and throat. He built up a large consultant practice and served on the staff of many hospitals inside and outside Liverpool, including the Royal Southern Hospital, the Eye and Ear Hospital, and the Alder Hey Children's Hospital. At the time of Munich, he gave up his practice and joined the Royal Air Force, and the outbreak of war found him medical officer in charge of a balloon-barrage

section. He was soon transferred to a post better suited to his qualifications on the research side of aviation medicine at the R.A.F. hospital at Ely. For his work on otitic barotrauma and allied problems he was appointed O.B.E. in 1944.

His main interest was bronchoscopy, and he was one of the pioneers of diagnostic endoscopy in this country. He contributed the section on this subject to Mr. W. G. Scott-Brown's textbook. About 1952 Mr. McGibbon succeeded to the lectureship in laryngology at Liverpool University. He retired from his hospital appointments about eighteen months ago.

J. M. writes:

"His colleagues knew that John McGibbon had had poor health for several years and had struggled on with his work. The struggle was an inspiration to us, and a lesson in will-power and courage. John was greatly admired. He was kind and wonderfully attentive to his patients, who literally flocked to see him from far and nearby. He belonged to the 'old school' and will be greatly missed."

Mr. McGibbon leaves a widow and a daughter.

ARCHIBALD PENMAN

M.D. Edin., D.P.H.

Dr. Penman, medical officer of health for Doncaster, died on Oct. 17 at the age of 58.

He qualified from the University of Edinburgh in 1923 and at once decided to join the public-health service. He took the D.P.H. in 1924, and the following year was appointed M.O.H. for Stirling. In 1927 he became assistant M.O.H. for Herefordshire. He went to Doncaster in 1935 as M.O.H. for the rural district, and in 1947 he was also appointed one of the first divisional medical officers in the West Riding.

J. F. writes:

"Archie Penman had a wide knowledge of public-health activities in a rural community and was always ready to place his experience at the service of his colleagues. For many years he was chairman of the care and after-care committee which looked after the welfare of persons with tuberculosis, and he will be sadly missed by its members. He was a delightful colleague with an unfailing sense of humour."

Dr. Penman leaves a widow.

ERNEST FAVENC CHIN

M.B. Sydney, F.R.C.S.

Mr. E. F. Chin, surgeon in charge of the thoracic unit at Southampton Chest Hospital and thoracic surgeon to other Hampshire hospitals, was killed in a motor accident on Dec. 5, when his car skidded and overturned on an icy road near his home at Nether Wallop. We hope to publish a biography and memoir next week, and in the meantime print the following personal tribute from T. H. S.:

"The main impact of the tragic death of Paul Chin lies not only in the feeling of personal loss among his friends but also in his loss to surgery. His name stands high among the younger generation of thoracic surgeons. Not only was he a fine surgeon in every sense of the word, but he had an extraordinary measure of enthusiasm and enterprise that put him in the class of born leaders. The Southampton chest clinic is a direct result of his efforts: in a few years it has become one of the busiest and most progressive centres in the country staffed by people who have been infected with his aims and ideals.

"When I first met him he had decided that his only possible future was to be in thoracic surgery, and of his subsequent years at Harefield I hold the happiest memories of a most stimulating and loyal colleague. When he was appointed to Southampton there was no doubt as to the future. Success came to the unit more rapidly than one had dared hope, and, though he would have been the first to admit his indebtedness to the work of others, it was his own efforts that predominated.

"Chin was a modern Elizabethan—gallant and adventurous with a fine physique and a slightly imperious presence. His personality was at the same time both attractive and challenging and his character was imbued with a sense of purpose, or even dedication, of an intensity that is all too rarely encountered. Loyalty and generosity he regarded and practised as among the major virtues. Basically he was a simple and genuinely modest man with a variety of interests outside surgery. At his home among his family he was at his best surrounded by people and the countryside he knew and loved well. It was on the journey to his home from hospital that he died."

Dr. H. B. NEWHAM

P. M.-B. writes:

"My arrival at the old London School of Tropical Medicine in 1909 coincided closely with Basil Newham's appointment as its third director and he soon made his influence felt. Though he made no claim to scientific eminence or to the performance of original work at that time, he had a flair for organisation and his teaching was direct and clear. There could be, moreover, no doubt about what he said or meant because his diction was remarkably clear. He had definite leanings towards the human and clinical side of tropical medicine, for he had been in practice for many years before he came under the spell of Patrick Manson and his tropical school. Newham was a friendly soul and a good mixer, so that his old students remembered this attitude."

Births, Marriages, Deaths

BIRTHS

GORDON.—On Nov. 3, to Nonette (Dr. Harris-Wright), wife of Ian J. Gordon, F.R.C.S., 217, Deakin Avenue, Mildura, Victoria, Australia—a third son, Alistair.

Appointments

BIRCH, E. W. G., M.B. Lond., D.P.H.: deputy M.O.H. and deputy principal school M.O., Lindsey.

CRAWSHAW, DORBEEN, M.B. Leeds: assistant M.O. (maternity and child welfare), Durham.

GODDARD, D. L. H., M.D. Lond., M.R.C.P.: deputy consultant physician-superintendent, Brompton Hospital, London (Frimley Branch).

HEGGIE, R. M., M.B., B.SC. Glasg.: medical superintendent, Cunard Steam-Ship Co., Ltd.

HOPPER, J. M. H., M.B. Durh., D.OBST., D.P.H.: senior school M.O., Northumberland.

KINSELLA, F. J. G., L.R.C.P.E.: M.O., health control unit, London Airport.

LOUGHLIN, J. V., M.B. N.U.I., D.P.H.: assistant M.O.H., Nottinghamshire, and M.O.H., Kirkby-in-Ashfield district.

REID, J. A. W., M.B. Glasg., D.P.H.: M.O.H., Helston, Camborne, Redruth, and Kerrier districts.

SHAW, W. M. H., M.B., B.SC. Leeds, F.R.C.S.: consultant plastic surgeon, General Infirmary, Leeds.

TURNER, WILLIAM, M.B. Leeds, LL.B. Lond., D.P.H.: M.O., Hyde.

Birmingham Regional Hospital Board:

FRASER JONES, JOHN, M.B. Lond., F.F.A.R.C.S.: consultant anæsthetist, Solihull and Little Bromwich hospitals.

SMITH, J. E. M., M.B. Calcutta, F.R.C.S.: consultant surgeon, Birmingham Accident Hospital.

TUDOR, R. W., CH.M. Birm., F.R.C.S.: consultant surgeon, Solihull Hospital.

Manchester Regional Hospital Board:

BRENNAN, C. M., M.B. Dubl., D.C.H., D.P.H.: assistant psychiatrist (S.H.M.O.), Calderstones Hospital.

CASHMAN, M. D., M.B. Durh., D.P.M.: assistant psychiatrist (S.H.M.O.), Lancaster Moor Hospital.

COBURN, J. G., M.D. Manc.: consultant dermatologist, Rochdale, Crumpsall and Booth Hall hospitals and Manchester and Salford Hospital for Skin Diseases.

ERULKAR, JOSEPH, M.B. Durh., M.R.C.P., D.P.M., D.C.H.: consultant child psychiatrist Booth Hall Hospital, Manchester.

GUNN, KERR, M.B. Edin.: assistant psychiatrist (S.H.M.O.), Whittingham Hospital.

North-Eastern Regional Hospital Board, Scotland:

LAWSON, I. R., M.D. Aberd.: S.H.M.O. in geriatrics, Aberdeen hospitals.

MACKENZIE, I. G., M.D. Edin., F.R.C.S.E.: consultant orthopædic surgeon, Aberdeen teaching hospitals.

SHORT, D. S., M.D. Cantab., PH.D. Lond., M.R.C.P.: consultant in general medicine, Aberdeen Royal Infirmary and Woodend General Hospital.

South-Western Regional Hospital Board:

AKEHURST, A. C., M.B. Lond., F.R.C.S.: consultant general surgeon, South Somerset clinical area.

HART, R. J., M.B. Lond., F.R.C.S.: consultant orthopædic surgeon, North Gloucestershire clinical area.

PARTRIDGE, J. P., M.B. Lond., F.R.C.S.: consultant surgeon, North Devon.

WILSON, T. G., M.D. Edin., M.R.C.P.E.: consultant neurologist, Devon and Cornwall.

Notes and News

HEBERDEN SOCIETY

AT the end of last week this society held its annual meeting in London. At the dinner in Apothecaries' Hall on Friday night the toast of The Society was proposed by Prof. W. Mansfield Cooper, vice-chancellor of the University of Manchester.

As a lawyer he regarded the invitation to speak as a friendly gesture from a profession still in the ascendant to one not quite what it was. But he detected a glimmer of a new dawn in the story of a worker who tripped over a lump of metal on the factory floor and broke his leg. "Don't move till I've brought the first-aid man", said his mate. "First-aid man be b . . . . . d," said the patient, "bring the shop steward!" "This," said Professor Cooper, "contains a wealth of comment on the rival contributions of your profession and mine." But the two professions, he always felt, had much in common—both being most vulnerable at their point of chiefest virtue. Both medicine and law lost their force unless placed at the service of those in need, wherever the need shows itself. Both were imbued by the principle of voluntary service; but doctors had found themselves unable to cope with the situation created by rising costs and new drugs and new methods of treatment. On balance, the National Health Service had been far more effective than the Legal Aid Scheme supposed to be its counterpart. On the medical profession fell the responsibility of defining a new professional ethic: the proper relationship of doctor and patient when in 95% of cases behind the patient stands an undisclosed partner—the State. Professor Cooper was sanguine of the result because he believed that, no matter what the pressure, the medical profession would base its doctrine not on the legal position of the doctor but on the needs of the patient.

Prof. J. H. Kellgren, replying as president, spoke of the encouragement given by the universities to people working in rheumatism.

In 1953 Manchester had created the first professorial department, and last year London had followed suit. In view of this progress in the universities, it was surprising how little had been done in the National Health Service—perhaps because universities were concerned with the enlargement of knowledge whereas the N.H.S. had to put service to patients first. To get a new specialty established in the N.H.S. one must arrive armed with gimmicks which only a specialist could use. But fortunately rheumatology did not follow these lines: the Heberden Society was not a body of rheumatologists banded together for professional aims but a body of physicians banded together for the advancement of knowledge. The increasing complexity of science required increasing horizontal specialisation by discipline but must have vertical integration by *problem*, comprising all disciplines. The society provided just that, ranging from biochemistry to epidemiology. Should it not in future contain also some non-medical specialists? Lately a new category had been created—the European member. The old barriers of distance and language were rapidly becoming obsolete and the Heberden Society should think of itself as European as well as British.

Prof. A. Neuberger, who had earlier given the Heberden oration, on the proteins of connective tissue, received the Heberden medal.

In thanking the society, he said that the most important changes in medicine in the past 20 or 30 years had been the result of scientific techniques not specifically based on medicine. Increasingly medical research tended to be divorced from hospitals, and to be done by people outside the profession. The main effort of medical schools must go into training good doctors, but they had the additional duty of advancing the knowledge of medicine in the broadest sense. Its advancement should not be entirely in the hands of people who have no connections with patients.

Sir Robert Platt, P.R.C.P., responding to The Guests, wittily proposed by Dr. R. M. Mason, took credit for the good idea that the first professor of rheumatology should be somebody who began by knowing nothing whatever about rheumatism, and secondly that he should be Dr. Kellgren. Heberden himself—though "I can't find that he wrote much about rheumatism"—attended Dr. Johnson in his last illness in 1784, and was called *ultimus Romanorum*. Even in those days each generation thought the next was less learned—perhaps because it was not learned in the right things.

MAKING MISTAKES

AT a meeting of the Section of General Practice of Manchester Medical Society on Nov. 23, Dr. A. M. COOKE (Oxford) gave an address On Making Mistakes. He emphasised three points: that mistakes were unfortunately inevitable; that this was no new problem, as shown by Roger Bacon's *De Erroribus Medicorum* written in the thirteenth century; and that a study of mistakes was one way of diminishing their incidence, especially because most of us were sufficiently Freudian to forget them. Stating his disapproval of the medical profession's love of classification, he went on to classify mistakes in various ways: those made by the profession as a whole, those made by patients, their relatives, doctors, nurses, technicians, and so on. He illustrated his remarks by many brief case-reports, some horrific and some amusing. He showed how mistakes could be made by ignorance, by patients deceiving doctors, wittingly or unwittingly, by inadequate histories, inadequate examination, misinterpretation of the clinical findings or laboratory tests, and typing errors. Some mistakes may seriously damage the patient, while others may save his life.

Dr. Cooke described the "observer error" in taking histories, examining the patient, and interpreting X-rays, and in laboratory investigations. He was strongly critical of abbreviations on the grounds that one's own abbreviations were sensible and quite clear, while other people's were foolish, obscure, and even dangerous. He mentioned the legal and ethical aspects of mistakes and concluded that although mistakes were inevitable, an occasional review of their causation was good for the doctor's soul and helped him to prevent them.

FACTS ALMOST UNLIMITED

UNLIKE some almanacks, Whitaker's does not officially forecast what will happen in the coming year. But all the same it seems to foretell with uncanny accuracy which are the facts and figures that a great many people will want to put their hands on during the next twelve months. Addicts can turn confidently to the latest edition [1] and will be delighted to find that it now includes lists of Acts passed during the last session of Parliament, satellites and moon rockets placed in orbit, the "leading" universities in the Commonwealth, and Olympic athletic records. New statistical tables strike a gloomier note, as is so often their way, and deal with such topics as prison populations, juvenile crime, and road casualties. The recent election results are given by constituencies, and Mr. Macmillan's new cabinet is to be found under the heading "Occurrences during Printing".

University of Oxford

On Nov. 28 the degree of D.M. was conferred on P. J. R. Nichols.

University of Cambridge

The Raymond Horton-Smith prize has been awarded to Dr. J. H. Angel and the Sir Lionel Whitby medal to Dr. P. B. C. Matthews.

On Nov. 28 the degree of M.B. was conferred on A. H. Abrahams (by proxy) and N. E. F. Lever.

University of Birmingham

The university has accepted the offer of ABC Television to present two closed-circuit television channels to the medical school. One camera will be permanently installed in an operating-theatre at the Queen Elizabeth Hospital, Birmingham; and a portable industrial television channel will be used for microscopy and behavioural research.

University of Wales

At recent examinations for the degrees of M.B., B.CH. the following were successful:

R. B. Griffiths, Maldwyn Hopkin-Thomas, Anne E. Jones, Morfydd R. Keen, J. E. Phillips, G. L. J. Roblings, Edith P. Thomas, Ann Varcoe, J. G. Wingfield.

International Congress on Nutrition

This congress will be held in Washington from Sept. 1 to 7. Further particulars may be had from the secretariat of the congress, 9650, Wisconsin Avenue, Washington 14, D.C., U.S.A.

1. London: Whitaker. Pp. 1190. 21*s*.

Royal College of Obstetricians and Gynæcologists

The diploma in obstetrics has been awarded to the following:

Mary M. Adlington, R. A. Aiken, D. I. Aitken, Robert Akroyd, M. R. Alderson, D. A. Andrewes, J. F. Andrewes, Elizabeth M. F. Andrews, J. W. H. Andrews, R. H. D. Andrews, R. St. J. Angel, E. J. Applegate, Saraswati Arora, C. R. N. Ashbee, D. L. Aspinall, B. J. Bartley, Nirmala Barua, J. M. Beazley, Janet I. Beggs, P. H. Beighton, Tiramiyu Belo-Osagie, J. T. Bench, Brian Bethell, Gerald Bevan, M. R. Bewsher, J. W. Blaxill, D. J. Blomley, B. H. Boeree, G. R. Bonner-Morgan, Elizabeth J. Bowen, R. D. Boyd, Richenda M. Breeze, R. K. Brennan, J. H. D. Briscoe, Andrew Brockmann, J. M. Brown, Gillian L. Browne, C. P. L. Bruggen, A. B. Bryan-Brown, I. F. M. Buchanan, T. A. S. Buist, D. A. O. Cairns, Rhoda J. Campbell, Gerald Cartmel, Kathleen M. Cash, P. A. F. Chalk, D. R. Chambers, P. J. Chambers, Beryl Collier, E. D. Colterjohn, A. P. Condie, Charlotte J. Crawford, B. J. Cremin, Rosemary L. Dart, A. G. Day, Susan J. de Graaff-Hunter, Ann C. Deuchar, Elizabeth M. Dixon, H. G. K. Douglas, Barry Dunn, A. J. B. Edwards, A. G. Edwards, Joan M. Edwards, J. I. Edwards, Nigel Edwards, Eugenia C. English, C. D. Evans, Gillian W. Evans, J. S. Evans, P. A. Farrelly, A. J. Ferris, D. R. Firth, P. N. Firth, P. W. Fisher, Rose A. Fisher, Freda M. Fletcher, J. G. R. Flint, G. F. Follett, John Frampton, D. R. Freebury, P. J. Fryer, P. M. Fullman, A. W. Galbraith, F. G. S. Gamm, E. B. Garner, P. W. Gasson, N. W. Glendinning, C. H. G. Gould, C. A. Gourley, A. M. Grant, A. E. G. Grace, D. R. Gunraj, Keith Hackett, C. I. Haines, D. S. Hall, M. J. Hannan, N. A. Harker, Rosalie M. Harrison-Bloom, V. J. Hartfield, H. A. Hartley, P. G. Hawker, D. C. Heap, J. G. Hendron, B. D. Hewitt, V. B. Hicks, P. G. Hickson, Joyce L. Hill, Mohan Vasudeo Hindlekar, Tin Tin Hmun, A. L. Hodgson, H. L. Hoe-Easton, J. J. Holden, R. J. Holden, C. D. Holdsworth, H. C. Hollingworth, E. J. Housley, B. J. Hovenden, E. S. Hughson, W. T. Hunter, J. M. R. Irving, Joseph Jacobs, Beryl Jameson, Irene R. Jamieson, P. M. Jeffreys, E. C. H. J. Josephides, Khalida Abdul Wahab Kayssi, I. W. Kemp, Christine M. L. Kerr, Jean J. Kerr, R. C. M. Kew, D. W. Keys, Talat Khan, Mahmooda Khatun, R. J. Knight, G. W. Knox, Bharati Kothary, J. M. J. F. D. Lalouette, R. W. Lamb, B. K. Lane, D. R. Laney, William Lang, Andrea M. D. Langford, Patricia A. Last, J. M. Laurent, B. E. Lee, S. G. Leech, Frances Lefford, I. G. Lennox, Elkan Lewis, Marina E. A. Lewis, D. Youn-Sen Liang, D. I. M. Linklater, J. B. Lloyd, J. L. Loakes, J. R. Lockwood, Nancy J. Logan, D. J. Longford, B. A. Lovell, A. D. Lower, Mary K. Lucas, A. P. Macdonald, H. N. Macdonald, K. J. Macdonald, Mary McDonald, K. L. McGeoch, Michael McGregor, Michael McKendrick, C. A. G. Mackenzie, H. M. Mackenzie, J. H. K. Mackie, D. S. McLean, Derek McLoughlin, Khursid Begum Mallick, R. M. H. Malone, L. V. H. Martin, D. R. Matthes, M. Yin May, Susan M. Mechie, Ashok Dattatraya Mehta, Maitray Markandrai Mehta, J. R. M. Millar, J. G. Miller, Geoffrey Mills, G. L. Mills, A. B. Milne, Robina W. Moar, P. E. Moffitt, R. M. Moffitt, Hilary M. Morgan, G. M. Morris, R. V. Morris, Sally Morris, J. G. M. Mortimer, Nicol Morton, Barbara A. Moss, P. M. Moss, Janice H. Mount, Jyostna Kumar Mukerji, M. E. Murray, Frances A. Musson, Chandatilleke Mutucumarana, J. J. Nel, R. E. D. Nelson, Sarah H. J. Nelson, Harold Nickson, H. G. Nicol, J. D. O. Noel, Hashim Abdul Rahim Noormahomed, Heather B. Nunnerley, Mercia Obadiah, B. B. Obeng, John O'Brian-Bell, Patrick O'Donnell, T. V. O'Dwyer, Margaret E. D. O'Flynn, Rita O'Hare, Ma Khin Ohn, H. W. L. Oliver, D. C. Ower, Stella M. Parrack, D. R. Parry, Marigold J. Parsons, M. H. Parsons, R. K. Pears, Gillian R. Perry, G. M. Petrie, I. G. Philip, B. L. D. Phillips, B. C. B. Pickles, A. M. M. Plumptre, J. S. Povey, R. C. Poyntz-Wright, Jennifer M. Radford, Arumugam Rajiyah, Leonard Ratoff, J. C. L. Rawes, A. A. Reid, E. F. Rice, Marion E. Richardson, S. R. Richardson, D. A. S. Robertson, J. E. Rogers, Edwina E. Rogerson, Margaret B. Ross, E. J. R. Rossiter, Barbara J. Rostron, Ryszard Mariqu Rumian, Catherine A. Ryan, P. R. Samsworth, G. J. Santer, J. H. Scotson, S. R. Scott, Urmil Sharma, D. B. Shaw, J. H. W. Shaw, D. J. Sills, I. D. Simpson, J. D. Simpson, A. J. Smellie, Brian Smith, Jacqueline A. K. Smith, P. R. Smith, J. W. Soper, R. N. Spencer-Gregson, M. C. Starks, J. A. Stevens, W. G. Stokes, D. J. Sutherland, Elizabeth M. Swanson, I. R. Swanson, Ignacy Swiestowski, Michael Taggart, Nargese Jehangir Talati, J. H. K. Taylor, R. G. Taylor, W. N. A. Taylor, D. W. P. Thomas, Edith H. Thomas, T. J. Tiplady, M. W. Tisdall, P. J. Toghill, R. J. Tolson, Jean E. Vallis, Prem Lata Vohra, Anne Y. M. Wadlow, George Wagner, J. W. Walker, Enid A. Wallace, D. M. Ward, Edna M. Watson, J. M. Watts, J. A. White, D. R. Whitehouse, Marian A. Wilkinson, M. K. Williams, Le Le Win, Julia M. Winter, J. S. Withey, J. A. Wood, T. C. Wood, D. W. Zutshi.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting on Nov. 27 with Mr. Arthur Jacobs, the president, in the chair, Mr. Hugh Fraser, Sir Alexander King, Sir John Parkinson, and Sir James Paterson Ross were admitted to the honorary fellowship.

Role of the Medical Officer of Health in Health Education

The Central Council for Health Education is holding a seminar on this subject from Feb. 23 to 26, at the Cora Hotel, Upper Woburn Place, London, W.C.1. Further particulars may be had from the medical director of the council, Tavistock House North, Tavistock Square, W.C.1.

Royal Photographic Society

After opening the exhibition of medical photography at the society's house, 16, Prince's Gate, London, S.W.7, on Nov. 12, Dr. Hugh Clegg, Editor of the *British Medical Journal*, presented awards as follows:

The *Lancet* trophy: Dr. Robert Ollerenshaw. The Association of British Pharmaceutical Industries trophy: Mr. A. L. Wooding. The Pharmaceutical Society's beginners' trophy: Mr. R. Morton.

The bronze medal given by the three Royal Colleges in London has been awarded by M. Vulmière, of Paris, for his work on photo-cine-endoscopic instrumentation. Work submitted or nominations for the next award should be sent to the hon. secretary, medical group, by Sept. 30.

New Burns Unit in Liverpool Region

Work is now beginning, at Whiston Hospital, Prescot, on a new unit with 32 beds for the treatment of burns and 43 for plastic surgery. The cost of the adaptations and extensions is estimated at £100,000, with a further £20,000 for furniture and equipment. The beds for burns in adults are intended to serve the whole of the Liverpool region and North Wales area.

The Biochemical Society will hold a meeting on Saturday, Dec. 19, at 10.30 A.M. at King's College Hospital Medical School, London, S.E.5.

The Chest and Heart Association is holding a symposium on pneumoconiosis on Friday, Jan. 29, at 10 A.M. at the Royal College of Science and Technology, Glasgow. Further particulars may be had from the association's Scottish office, 65, Castle Street, Edinburgh 2.

In the New Year, Dr. C. W. M. Whitty is to visit Australia for two months, during which he will deliver in Adelaide a memorial lecture to the Hugh Cairns Society.

The name of 'Kappaxan' (kanamycin, Bayer Products, Ltd.) has been changed to 'Kannasyn'.

'Atrol' (diethylaminoethanol), introduced last year by Messrs. Duncan, Flockhart & Co., Ltd., for clinical trial, has been withdrawn from the market.

British Standards have been published for (i) characteristics and method of test of air conduction hearing-aids using electronic amplification (B.S. 3171, 1959, 4*s.* 6*d.*) and (ii) eustachian catheters (B.S. 3163, 1959, 3*s.*). Copies may be obtained from the British Standards Institution, 2, Park Street, London, W.1.

Diary of the Week

DEC. 13 TO 19

Sunday, 13th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
10.15 A.M. Mr. William McKenzie: Common Ear, Nose, and Throat Diseases.

Monday, 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Richard Doll: Ætiology of Bronchial Carcinoma.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5 P.M. Dr. Rudi Schmid (Boston): Bile Pigments.
HUNTERIAN SOCIETY
7.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Dr. Thomas Hunt, Dr. R. M. B. MacKenna, Dr. Henry Wilson: Itching Skin.
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Mr. T. B. FitzGerald: History is Bunk.

Tuesday, 15th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. E. H. Belcher: Functional Tests with Radioisotopes.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Mr. B. N. Brooke: Ulcerative Colitis.
SOUTH-WEST LONDON MEDICAL SOCIETY
8.45 P.M. (Tooting Bec Hospital, S.W.17.) Dr. J. E. S. Lloyd: Admission to Mental Hospital and New Legislation.
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Prof. I. A. Richmond: Roman Army Medical Service.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. C. S. Hallpike: Pathology and Differential Diagnosis of Organic Affections of the Eighth Nerve System.

Wednesday, 16th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Comparative Medicine.* Prof. K. R. Hill, Mr. L. M. Markson, Dr. R. Schoental: Senecionsis in Man and Animals.
8.15 P.M. *General Practice.* Dr. F. H. Staines, Miss L. J. Gray, Miss A. Graham, Dr. J. E. Haine: Cooperation in General Practice.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Prof. J. Z. Young, Dr. Macdonald Critchley, Dr. R. S. Allison: Memory.
EUGENICS SOCIETY
5.30 P.M. (Royal Society, Burlington House, W.1.) Dr. C. F. Blacker: Birth Control and Sterilisation in Asian Countries with Special Reference to Japan and India.

Thursday, 17th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. R. M. H. McMinn: Cellular Anatomy of Experimental Wound Healing. (Arris and Gale lecture.)
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Sir Wilfrid Sheldon: Problems in Training and Educating Children.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh, 8.) Sir Dugald Baird: The Place of Epidemiology in Obstetrical Research.

Friday, 18th

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Edinburgh, 8
3.30 P.M. Sir Victor Negus: Ciliary Action.